American Heart Journal

An international publication for the study of the circulation

George E Burch *Editor*

Thomas D Giles *Assistant Editor*

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JULY DECEMBER 1977

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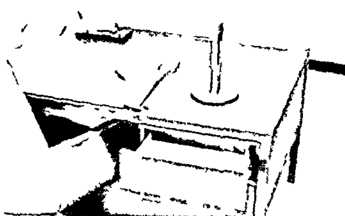
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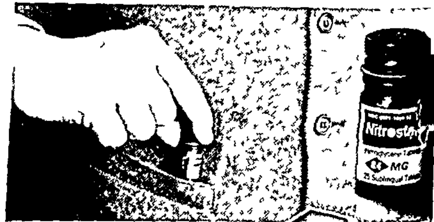
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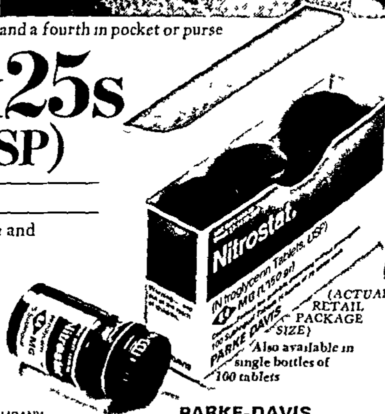
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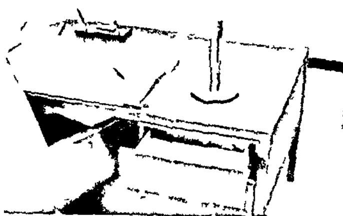
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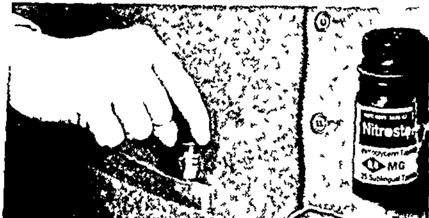

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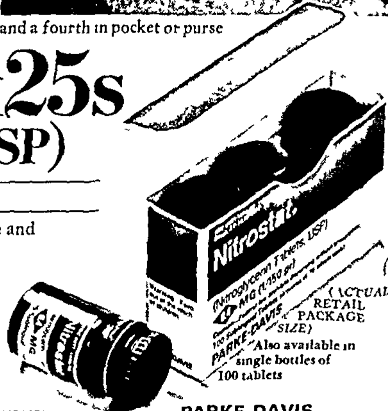
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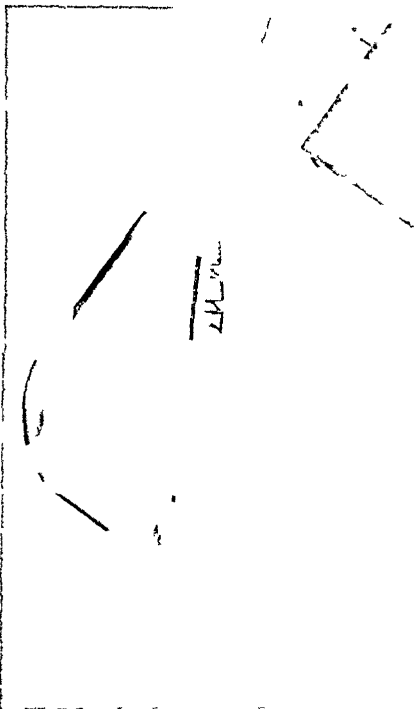
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American Heart Journal

July 1977 Volume 94 Number 1

Editorial

Technocrats or doctors?

George E Burch M D
New Orleans La

Unfortunately too many physicians who are trained today to care for the sick seem to be more technocrat than doctor This is probably exemplified better by the field of cardiology than by any other field of medicine Patients are often subjected to unnecessary expensive and hazardous procedures in diagnosis and treatment more at present than ever before even when simple ordinary office and bedside procedures are adequate Regrettably many in the health field are led to believe not only that complex and expensive procedures are necessary for good medical practice but that there is no other way to provide good and acceptable care These physicians fail to realize that the doctor with his five senses and good clinical training can render better service to his patients without hazard and with considerably less expense to the patient and his insurance and government financing agencies than can the new technocrats Apparently the new physician believes that if he cannot manage a cardiac patient well with his own five senses no one else can Yet this same technocrat will readily admit that there are master and superior violinists singers dancers composers and artists He readily accepts the fact that these people are trained to render masterful performances and productions whereas others remain amateurs But he will not accept the fact that this is also true in office and bedside cardiology This attitude unfortunately reflects present day undergraduate and specialty training With effort and proper training physicians can become masters in bedside and office cardiology

It is truly pathetic when a physician has to measure the left ventricular end diastolic pressure by cardiac catheterization before he can recognize with confidence left ventricular congestive heart failure or when he must obtain an echocardiogram and catheterize a patient to know when the patient has aortic stenosis and aortic valve regurgitation Any well trained cardiologist can make these diagnoses readily at any time at the bedside or in his office and also note changes from moment to moment without imposing any expensive and hazardous studies upon his patient Furthermore these complex procedures are one or two time procedures anyway whereas the bedside approach is applicable from moment to moment and always simple to employ Those who resort to cardiac catheterization are using poor and erroneous technics with rare exceptions and the data are usually not quantitatively accurate

In some hospitals large centers and medical practices patients with chest pain even extracardiac pain are routinely subjected to echocardiography vectorcardiography treadmill stress test coronary angiography left ventricular catheterization lung scan and all sorts of chemical and other expensive cardiac studies Such routine practice cannot be condoned Surely there are specific indications for each of these and other special procedures but the indications are rare and certainly not routine Furthermore the well trained clinical cardiologist knows when each is indicated and where accurate studies can best be

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Pulmonary valve fluttering in subpulmonic ventricular septal defect

Stephen P Glasser M D *
Ralph W Baucum Jr M D **
Tampa Fla and Shreveport La

The diagnostic value of the echocardiographic motion of the pulmonary valve has been expanding Recently Weyman and associates[1,2] described the echocardiographic patterns of pulmonic valve motion in pulmonary hypertension and in the differentiation of infundibular from valvular pulmonic stenosis Specifically in this latter instance a marked chaotic systolic fluttering of the pulmonary valve leaflet was recorded in patients with infundibular pulmonic stenosis They postulated that the fluttering was due to the turbulent stream of blood distal to the obstruction This report describes the pattern of pulmonary valve motion in three patients with clinically diagnosed subpulmonic ventricular septal defect with no evidence at catheterization of infundibular pulmonic stenosis in which a similar type of systolic coarse fluttering of the pulmonic valve was recorded We have not seen this pattern in other types of ventricular septal defect

Materials and methods

Echocardiographic tracings of the pulmonary valve were examined in patients with catheterization documented ventricular septal defect and no infundibular outflow obstruction The diagnosis of subpulmonic ventricular septal defect was made on the basis of a murmur with characteristic location and radiation[3] (in all patients the murmur suggested infundibular pulmonic stenosis as an alternate consideration) the lack of a pressure gradient at the right ventricular outflow tract or at the pulmonic valve level and documentation of a left to right shunt at the ventricular level

The echocardiographic examination was performed with an Ekoline 20A echograph combined with a Honeywell model 1856 fiber optic strip chart recorder utilizing a 2 25 MHz transducer focused at 7 5 cm The pulmonic valve was examined using the technique described by Gramiak and colleagues[4]

These findings were compared with pulmonic valve motion in 16 cases of catheterization documented ventricular septal defect other than the subpulmonic type Table I summarizes the pertinent clinical and hemodynamic data

Results

Normal pulmonary valve motion has been previously described Briefly the valve moves posteriorly with onset of systole (Fig 1 b c) then moves anteriorly during systole (Fig 1 c d) followed by rapid diastolic closure (Fig 1 d e) The leaflet then moves posteriorly to point f (Fig 1) With atrial contraction there is again a brief posterior motion (a wave) whereupon the leaflet returns to a closed position (point b Fig 1) Fine fluttering of the pulmonary valve can be a normal phenomenon but when present does not extend beyond pulmonary valve closure

In the three cases of subpulmonic ventricular septal defect the posterior pulmonic valve leaflet opened and closed normally but during its open position there was a coarse chaotic fluttering present (Fig 2) A max and the e f (Fig 1) slope were normal in the three cases of subpulmonic ventricular septal defect as well as in other types

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obtained Were patients carefully and critically followed at autopsy, a great deal would be learned about the reliability of good office and bedside cardiology and there would be less need for complex, hazardous, and expensive studies

Are we training and supporting technocrats instead of clinicians? We need to train doctors for the day to day office practice and bedside medicine These doctors should be trained to know when and where to refer their rare patients who truly need special studies The cost of cardiologic care would decrease precipitously, serious and fatal accidents due to these studies would practically disappear, the cardiac patient and his family would be happier, costs for service would decline markedly, and the medical profession would be admired even more were doctors trained to render excellent service in the office and at the bedside

Clinical communications

Pulmonary valve fluttering in subpulmonic ventricular septal defect

Stephen P Glasser M D *
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The echocardiographic examination was performed with an Ekoline 20A echograph combined with a Honeywell model 1856 fiber optic strip chart recorder utilizing a 2.25 MHz transducer focused at 7.5 cm. The pulmonic valve was examined using the technique described by Gramiak and colleagues.[5]

These findings were compared with pulmonic valve motion in 16 cases of catheterization documented ventricular septal defect other than the subpulmonic type. Table I summarizes the pertinent clinical and hemodynamic data.

Results

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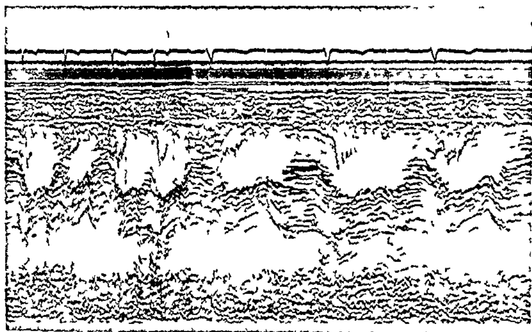


Fig 2 Representative section of the pulmonic valve echogram from Patient No 2 The sweep speed is increased midway through the recording

reliable the echocardiographic feature of pulmonic valve fluttering will be shall depend on further studies

Summary

Three patients with subpulmonic ventricular septal defect and pulmonary valve fluttering by echocardiography are presented The echographic changes appear identical to that reported with infundibular pulmonic stenosis and the mechanism causing this fluttering is probably similar

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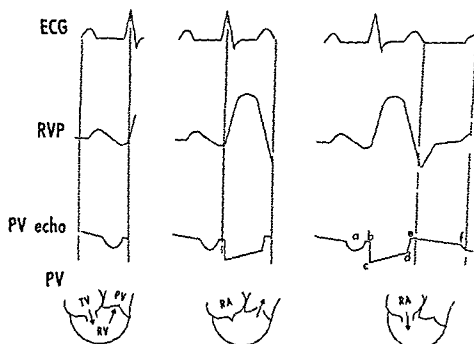


Fig 1 A diagramatic representation of the pulmonary valve echogram *(PV echo)* as it relates to the electrocardio gram *(ECG)* right ventricular pressure *(RVP)* and the relative location of the pulmonary valve *(PV)*

Table I Patient data

Case	*Age (yrs)*	*Loudest murmur*	*Maximum thrill*	*Pressures*			*L→R shunt (oximetry)*	*RV H_t*	*Angiography*
				RA (mean)	*RV*	*PA*			
C R	15	2nd LICS	2nd LICS	–	30/0 10	30/10	1 4 to 1	+	L → R shunt at ventricular level
J.S	18	2nd LICS	2nd LICS	7	34/0 8	32/10	1 6 to 1	+	L → R shunt at ventricular level
J B	1	2nd LICS	2nd LICS	5	55/0 8	50/12	3 to 1	+	L → R shunt at ventricular level

This patient also had aortic regurgitation
†All murmurs radiated to the neck

of ventricular defect included in our study group However in the latter instance no significant fluttering has been observed

Discussion

The characteristic finding in the three patients with subpulmonic ventricular septal defect reported herein was a coarse, somewhat chaotic fluttering of the pulmonary valve We assume a similar mechanism as that postulated by Weyman and co workers [2] namely a turbulent stream of blood striking the pulmonary valve In two patients the septal defect was small but in the third patient the pulmonary flow was three times systemic No other differentiating features were noted in pulmonary valve motion 'a" wave depth and e f slope (Fig 1) was similar in all types of ventricular septal defect Clinical differentiation of subpulmonic ventricular septal defect from infundibular pulmonic stenosis may prove difficult since pulmonary valve fluttering may be seen in both Echocardiographic differentiation may be impossible In severe infundibular stenosis the a wave may be absent however in mild infundibular stenosis a wave depth may be normal However when ventricular septal defect is suspected clinically or documented at cardiac catheterization the presence of pulmonary valve fluttering suggests a subpulmonic location As noted the three patients were diagnosed by the classical clinical findings of subpulmonic ventricular septal defect,[3, 4] the presence of a left to right shunt and the absence of infundibular pulmonic stenosis at the time of catheterization How

Table I Characteristics of furosemide recipients

Characteristics	*Per cent of patients*
Age	
Less than 40 years	5 7
40 to 59 years	30 1
60 to 69 years	27 3
[illegible]0 years or older	36 9
Total	100 0
Sex	
Male	57 0
Female	43 0
Total	100 0
Survival	
Survived	83 7
Died	16.3
Total	100 0
Duration of hospitalization	
Less than 10 days	30 8
10 to 19 days	38 6
[illegible]0 days or more	30 6
Total	100 0
Admission BUN level (mg per 100 ml)	
Less than 25	59 4
25 to 49	26.5
50 to 99	8 5
100 or more	2 7
Not specified	2 9
Total	100 0

total furosemide dose was more than 450 mg 42 4 per cent of patients received one or more doses of furosemide by parenteral routes the rest received it only by the oral route (Table III) The clinical efficacy of furosemide was judged to be unsatisfactory in 8 per cent of cases

Combination drug therapy for fluid retention cardiac disease hypertension or neoplastic disease was common (Table III) Nearly two thirds of furosemide recipients were treated with potassium supplements or potassium sparing diuretics during or prior to their exposure to furosemide Digitalis glycosides were administered to 69 2 per cent of furosemide treated patients

Adverse reactions Adverse reactions were attributed to furosemide in 239 (10 1 per cent) of the 2 367 patients (Table IV) In all instances both the attending physician and the clinical pharmacologist who later reviewed the case judged that the adverse reaction was probably or definitely due to furosemide either entirely or in part In 162 cases a specific therapeutic measure

Table II First discharge diagnoses among 2 367 furosemide recipients

Diagnosis	*No of patients*	*Per cent of patients*
Cardiac disease		44 4
Acute myocardial infarction	164	
Other ischemic heart disease	330	
Congestive heart failure	320	
Rheumatic heart disease	134	
Other	104	
Total	1 05[illegible]	
Other cardiovascular disease		9 0
Peripheral vascular disease	75	
Cerebrovascular disease	61	
Hypertension	52	
Other	26	
Total	214	
Pulmonary disease		12 0
Obstructive pulmonary disease	151	
Pulmonary infection	101	
Other	3[illegible]	
Total	284	
Hepatic disorders		5 6
Cirrhosis	113	
Other	20	
Total	133	
Neoplastic disease	174	7 4
Renal disease	98	4 1
Endocrine disease	[illegible]0	3 8
Gastrointestinal disease	50	2 1
Other	[illegible] 2	11.5
TOTAL	2,367	100 0

(i e discontinuation or reduction in dosage of furosemide administration of potassium supplements infusion of fluid and solute etc) was instituted by physicians immediately following the adverse reaction

Untoward effects of furosemide were considered life threatening in 14 instances (Table V) Eight of these 14 patients died but in only two cases did attending physicians judge that furosemide contributed to the patient s death (Case Nos 8 and 13 Table V) Both of these individuals were elderly had serious or terminal underlying diseases and were receiving other drugs which influence fluid and electrolyte balance

Volume depletion Manifestations of intravascular volume depletion were the most common type of adverse reaction attributed to furosemide reported in 109 patients (4 6 per cent) (Table IV) A rise in BUN either alone or together with another adverse reaction was the most frequent

Clinical toxicity of furosemide in hospitalized patients

A REPORT FROM THE BOSTON COLLABORATIVE DRUG SURVEILLANCE PROGRAM

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Furosemide a highly effective diuretic agent[1-4] has been marketed in the United States since 1966 A variety of untoward effects primarily electrolyte disturbances and volume depletion have been attributed to the drug[1-6] but little is known about the frequency of such effects or the factors predisposing to them The present report describes adverse reactions to furosemide observed among 2 367 hospitalized patients treated with the drug

Patients and methods

The scope and operation of the Boston Collaborative Drug Surveillance Program have been described previously[7-9] Trained nurse monitors stationed on medical wards use standardized self coding sheets to record information on consecutively admitted patients Data are collected on patient characteristics diagnoses, the therapeutic efficacy of all drugs administered, details of dosage, and duration of therapy When drug treatment is instituted, the prescribing physician is interviewed to determine the therapeutic indications Reasons for termination of therapy and descriptions of possible adverse reactions are recorded as well For each suspected adverse drug reaction, the attending physician judges the likelihood that the drug caused the adverse reaction An independent second judgment is later rendered by a clinical pharmacologist who reviews the case

This report is based on data accumulated between 1966 and 1973 on 17,068 hospitalized medical patients in the United States Canada, Israel, and New Zealand of whom 2,367 (13 9 per cent) received furosemide

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Results

Patient characteristics More than one third of the 2 367 furosemide recipients were over 69 years of age and 16 3 per cent died in the hospital (Table I) Moderate or severe renal insufficiency as judged by admission blood urea nitrogen (BUN) levels of 50 mg per 100 ml or greater was present in 11 2 per cent of patients More than half of the patients had a primary (first) discharge diagnosis of cardiovascular disease (Table II)

Furosemide therapy Congestive heart failure was the most common indication for furosemide treatment (Table III) A wide range of doses was administered, in 21 4 per cent of cases the mean daily dose exceeded 55 mg and in 29 per cent the

Table V Life threatening adverse reactions to furosemide as judged by attending physicians

Case	*Age*	*Sex*	*Diagnoses*	*Description of event*
1	88	F	Hypertension Congestive heart failure Pneumonia Thrombocytopenia	Developed thrombocytopenia (platelet count = 88 000/mm) following therapy with digitoxin hydrochlorothiazide ampicillin and furosemide Died after 10 days of hospitalization. Multiple points of gastrointestinal hemorrhage found at autopsy
2	67	F	Thrombophlebitis Pulmonary embolism	Rise in BUN (to 40 mg /100 ml) and uric acid (to 8.9 mg /100 mL) after 12 days of furosemide treatment Died of other causes 2 days later
3	64	M	Mitral stenosis Congestive heart failure	Developed hypochloremia (chloride = 75 mEq /L.) and alkalosis (bicarbonate = 40 mEq /L.) 2 to 4 days after starting furosemide Became anxious and confused Recovered following administration of potassium and ammonium chlorides
4	33	F	Diabetes mellitus Psoriasis	Severe hypokalemia (potassium = 1.8 mEq /L.) during treatment with furosemide and insulin despite concurrent administration of potassium chloride and spironolactone
5	75	M	Chronic renal failure Anemia Pulmonary edema	Worsening azotemia (BUN rise from [illegible] to 110 mg /100 mL) hyperkalemia (potassium = [illegible]2 mEq /L.) and acidosis (blood pH = [illegible] 17) during treatment with furosemide 80 mg daily for 3 days
6	67	F	Esophageal varices Pleural effusion	Experienced *1,500 mL diuresis during 5 hr after 40 mg intravenous* dose of furosemide Became severely hypotensive (systolic BP 70 mm Hg) Recovered from this episode
7	46	F	Cirrhosis Hepatorenal syndrome	After 4 days of furosemide (80 mg /day) developed asterixis impaired mental status hyponatremia (sodium = 118 mEq /L.) *and alkalosis* (bicarbonate = 38 mEq /L.) Recovered from this episode
8	71	M	Reticulum cell sarcoma Pneumonia	Received antineoplastic agents and several diuretics including 3 days of furosemide (40–120 mg /day) Became dehydrated hyponatremic (sodium = 111 mEq /L.) hypochloremic (chloride = 80 mEq /L.) febrile and died 9 days after furosemide was stopped
9	59	M	Emphysema Congestive heart failure Pneumonia Renal failure	Received intravenous or oral furosemide on several occasions After a 40 mg intravenous dose diuresis exceeding 2,000 mL ensued over [illegible] hr Became hypotensive (BP 85/65 mm Hg) and oliguric Recovered following infusion of mannitol
10	59	M	Staphylococcal septicemia Bacterial endocarditis Congestive heart failure	Two days after a single 40 mg intravenous dose of furosemide developed hypokalemia (2.7 mEq /L.) and cardiac arrhythmias *consistent* with digitalis toxicity Recovered *from this event* but died 6 days later
11	55	M	Congestive heart failure	After 37 days of oral furosemide (40 mg /day) became anorectic lethargic and hypokalemic (2.9 mEq /L.) *Recovered* without sequelae
12	54	M	Chronic obstructive pulmonary disease Cor pulmonale	Received oral furosemide (140–360 *mg /day) for 30* days and developed *severe metabolic alkalosis superimposed* upon respiratory acidosis
13	86	F	Diabetes mellitus Congestive heart failure	After 8 days of oral and *intravenous furosemide* therapy developed hypokalemia (potassium = *2.8 mEq /L.) and* alkalosis (bicarbonate = *47 mEq /L.)* Died 2 days later of intractable CHF and elec*trolyte imbalance*
14	61	M	Chronic alcoholism Cirrhosis Ascites	Eight days after single 40 mg oral dose *of furosemide* had become hypochloremic (chloride = *86 mEq L.)* alkalotic (bicarbonate = 39 mEq L.) and experienced a rise in BUN from 24 to 66 mg /100 mL

tailed test) than among those receiving furosemide alone (26 8 mg per 100 ml)

Hypokalemia Clinically important hypokalemia as judged by attending physicians was attributed to furosemide in 85 recipients (3 6 per cent) (Table IV) In 20 cases it was associated with volume depletion or with another electrolyte abnormality and in three cases it occurred with a cardiac arrhythmia In 67 instances serum potassium levels were available prior to furosemide therapy and at the time of the adverse reaction The mean fall in serum potassium was 1 1 mEq per liter (range 0 2 to 2 8 mEq per liter)

Hypokalemia was attributed to furosemide *in 46 of the* 1,533 patients (3 0 *per cent*) who concurrently received potassium supplements (i e potassium chloride) or potassium sparing diuretics (triamterene *spironolactone*) but in 39 of the

Table III Characteristics of furosemide therapy

Characteristic	Per cent of patients
Indication for therapy	
Congestive heart failure	77 7
Fluid retention due to cirrhosis	7 7
Fluid retention due to neoplastic disease	1 9
Hypertension	1 4
Anuria	0 1
Other and unspecified	11 2
Total	100 0
Total dose of furosemide	
Less than 100 mg	34 4
100 to 450 mg	30 3
451 mg or more	29 1
Could not be calculated	6 2
Total	100 0
*Daily dose of furosemide**	
Less than 35 mg	36 8
35 to 55 mg	33 6
56 mg or more	21 4
Could not be calculated	8 2
Total	100 0
Route of furosemide administration	
Intravenous	35 5
Intramuscular	6 9
Oral only	56 7
Not specified	0 9
Total	100 0
Drug therapy concurrent with furosemide†	
Other potassium wasting diuretics (thiazides mercurials ethacrynic acid etc)	23 4
Potassium supplements or potassium sparing diuretics (i e potassium chloride spironolactone triamterene)	64 8
Digitalis glycosides	69 2
Corticosteroids or antineoplastic agents	15 7
Antihypertensive drugs (methyldopa hydralazine guanethidine clonidine diazoxide etc)	7 3

Calculated as the total dose divided by the number of days of therapy

†*Many patients received more than one class of drug concurrently*

consequence observed In 91 cases BUN values were available prior to furosemide therapy and at the time of the adverse reaction The mean rise in BUN for these patients was 30 8 mg per 100 ml (range 7 to 122 mg per 100 ml)

The frequency and severity of volume depletion attributed to furosemide was influenced by coadministration of other diuretic agents Among 553 patients who received other diuretics prior to or during furosemide treatment 49 (8 9 per cent) developed volume depletion among those not receiving other diuretics the frequency was 3 2 per cent (χ = 28 5 d f = 1 p < 0 001) The mean rise in BUN for those volume depleted patients who received other diuretics in addition to furosemide (35 8 mg per 100 ml) was significantly greater (unpaired t = 2 04 p = 0 05 two

Table IV Adverse reactions to furosemide

Adverse reactions	No of patients	Per cent of patients
Volume depletion		4 6
Elevation in BUN or serum creatinine only	68	
Elevation in BUN with other adverse reactions*	27	
Hyponatremia or hypochloremia	(12)	
Hyperuricemia	(6)	
Hypotension	(4)	
Hyperglycemia	(2)	
Gastrointestinal disturbance	(2)	
Alkalosis	(1)	
Other manifestations of volume depletion	14	
Hypotension†	(10)	
Excess diuresis or loss of body weight	(4)	
Total	109	
Hypokalemia		3 6
As the only manifestation of toxicity	59	
With other adverse reactions	26	
Hyponatremia or hypochloremia	(16)	
Volume depletion	(4)	
Cardiac arrhythmia	(3)	
Gastrointestinal disturbance	(3)	
Total	85	
Electrolyte or metabolic disturbances‡		1 5
Hyponatremia	11	
Hypochloremia	1	
Hyponatremia and hypochloremia	12	
Hyperuricemia	8	
Metabolic alkalosis	3	
Hyperglycemia	1	
Total	36	
Other adverse reactions		0 4
Rash	4	
Central nervous system disturbances	3	
Flushing	1	
Dry mouth	1	
Total	9	
Total with adverse reaction	239	10 1

Does not include four patients with volume depletion and hypokalemia (see under *Hypokalemia*)

†Does not include four patients with elevation in BUN and hypotension

‡Does not include patients with electrolyte or metabolic disturbances together with hypokalemia or volume depletion

Table V Life threatening adverse reactions to furosemide as judged by attending physicians

Case	*Age*	*Sex*	*Diagnoses*	*Description of event*
1	88	F	Hypertension Congestive heart failure Pneumonia Thrombocytopenia	Developed thrombocytopenia (platelet count = 88 000/mm) following therapy with digitoxin hydrochlorothiazide ampicillin and furosemide Died after 10 days of hospitalization Multiple points of gastrointestinal hemorrhage found at autopsy
2	[illegible]7	F	Thrombophlebitis Pulmonary embolism	Rise in BUN (to 40 mg /100 ml) and uric acid (to 8 9 mg /100 ml.) after 1[illegible] days of furosemide treatment Died of other causes 2 days later
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5	75	M	Chronic renal failure Anemia Pulmonary edema	Worsening azotemia (BUN rise from 5[illegible] to 110 mg /100 ml.) hyperkalemia (potassium = 7.2 mEq /L.) and acidosis (blood pH = 7 1[illegible]) during treatment with furosemide, 80 mg daily for 3 days
6	6[illegible]	F	Esophageal varices Pleural effusion	Experienced 1,[illegible]00 ml diuresis during 5 hr after 40 mg intravenous dose of furosemide Became severely hypotensive (systolic BP [illegible]0 mm Hg) *Recovered from this episode*
7	46	F	Cirrhosis Hepatorenal syndrome	After 4 days of furosemide (80 mg /day) developed asterixis impaired mental status hyponatremia (sodium = 118 mEq /L) and alkalosis (bicarbonate = 38 mEq /L.) Recovered from this episode
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tailed test) than among those receiving furosemide alone (26 8 mg per 100 ml)

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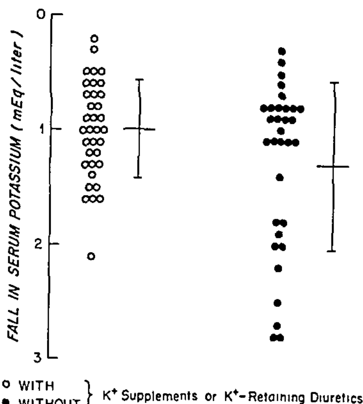


Fig 1 Fall in serum potassium concentrations among patients with hypokalemia attributed to furosemide divided according to whether they received or did not receive concurrent or prior therapy with potassium supplements or potassium retaining diuretics Individual values and means (± standard deviation) are shown

839 patients (4 6 per cent) who received furosemide without such supplements ($\chi^2 = 3.91$ d f = 1, $p < 0.05$) In addition, the mean drop in serum potassium among the supplemented' hypokalemic furosemide recipients (1 0 mEq per liter) was significantly less ($t = 2.00$ $p \simeq 0.05$ two tailed test) than among the nonsupplemented (1 3 mEq per liter) (Fig 1) Hypokalemia also developed more slowly in patients receiving potassium supplements or potassium retaining agents (Fig 2) It was reported within the first 5 days of therapy in 76 per cent of the nonsupplemented hypokalemic cases, but in only 31 per cent of those receiving the supplements

Other adverse reactions Other types of electrolyte or metabolic disorders were observed as the primary manifestations of toxicity in 1 5 per cent of recipients and as secondary or coincident findings in many other instances (Table IV) Hyponatremia, hypochloremia, or both were reported alone in 24 cases and together with other adverse reactions in 28 cases At the time of the adverse reaction the mean serum sodium level was 125 6 and the serum chloride 85 5 mEq per liter Hyperuricemia was the major manifestation of furosemide toxicity in eight patients (0 3 per cent), two of whom experienced acute gouty arthritis In six other cases, hyperuricemia was associated with volume depletion The mean serum urate level at the time of detection of hyperuricemia was 11 5 mg per 100 ml

Factors influencing the frequency of adverse reactions As discussed above, potassium supplementation and coadministration of other diuretics correlated with the frequency of hypokalemia and volume depletion Furosemide dosage correlated with the over all frequency of reported toxicity (Fig 3) Adverse reactions increased progressively in frequency from 5 2 per cent in those receiving less than 35 mg per day to 18 8 per cent in those receiving more than 55 mg daily (test for linear trend $\chi = 63.4$ d f = 1 $p < 0.001$) A similar relation was observed when specific adverse reactions were analyzed individually

Age, sex, survival admission BUN serum albumin level, body weight, indication for furosemide therapy, route of administration total dose of furosemide coadministration of antineoplastic drugs, and coadministration of antihypertensive agents were not significantly related to the frequency of adverse reactions to furosemide

Discussion

The present study summarizes in quantitative terms the unwanted effects of furosemide among 2 367 intensively monitored hospitalized medical patients Estimates of toxicity are derived from clinical judgments made by attending physicians These judgments are generally based upon the pharmacologic properties of the drug and the time relation between drug exposure and the unwanted clinical effect An independent evaluation of each episode by a clinical pharmacologist was used to support the judgments of attending physicians

Our results must be interpreted in light of the complex clinical circumstances in which furosemide was administered The drug was used to treat a variety of fluid retention states secondary to cardiac renal hepatic or neoplastic disease and was commonly coadministered with other drugs that influence fluid and electrolyte balance It is often difficult to assess the relative contributions of each drug when an unwanted clinical

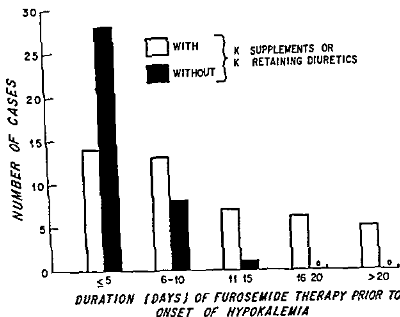


Fig 2 Duration of furosemide therapy prior to onset of hypokalemia in patients with hypokalemia attributed to furosemide Cases are divided into those who received and who did not receive concurrent or prior therapy with potassium supplements or potassium retaining diuretics

event is observed in a patient receiving multiple drug therapy Finally the severity of underlying disease among furosemide recipients ranged from relatively minor to life threatening or terminal

Despite these complexities the present study appears to provide useful quantitative information on the clinical toxicity of furosemide in hospitalized medical patients In general the data are reassuring since serious toxicity was unusual Adverse reactions were attributed to the drug in 239 patients (10 1 per cent of all recipients) but in only 14 instances was the toxic event considered life threatening Furosemide appeared to contribute to the death of only two individuals both of whom had serious or terminal underlying diseases and were receiving other drugs concurrently Adverse reactions to furosemide were more frequent with higher daily doses consistent with the dose dependent diuretic effect of the drug[2,3] [1] However the frequency of unwanted reactions was not correlated with the total dose of furosemide suggesting that the drug produces no cumulative toxicity No influence of the route of administration on the frequency of adverse reactions was detected although oral furosemide is incompletely absorbed in many patients[2,11] The presence of renal insufficiency as judged by admission BUN levels also did not influence the frequency of unwanted effects This

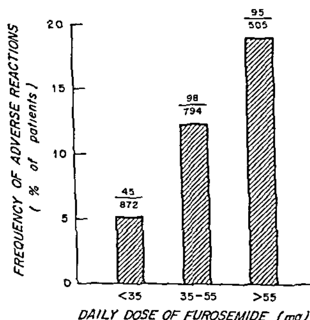


Fig 3 Frequency of adverse reactions to furosemide in relation to the daily dose

suggests that furosemide carries no substantial additional hazard in patients with renal disease [5] possibly because nonrenal clearance of the drug is sufficient to prevent its cumulation.

Intravascular volume depletion was the most common type of adverse reaction attributed to

furosemide It occurred in about 5 per cent of recipients, and was usually manifested as a rise in BUN The diuretic effectiveness of furosemide probably accounts for unintended volume depletion although increased venous capacitance[16] and decreased cardiac output[1] may contribute to hypotension in some patients Coadministration of other diuretics was associated with a higher frequency and possibly a greater extent of volume depletion

Clinically important hypokalemia was reported as an adverse reaction to furosemide in 4 2 per cent of recipients Coadministration of potassium supplements or potassium retaining diuretics did not completely prevent hypokalemia but did appear to reduce its frequency and severity and to delay its onset This might be a spurious finding due to more intensive physician monitoring of the nonsupplemented patients but it is more likely that prophylactic potassium supplementation or coadministration of potassium sparing agents does in fact reduce the frequency and severity of diuretic induced hypokalemia However the widespread need for potassium supplementation during diuretic therapy is not established and it is unclear whether the benefits outweigh the risks Not all patients receiving diuretics experience depletion of total body potassium and such depletion may be present without hypokalemia Furthermore, administration of potassium chloride or spironolactone carries the risk of hyperkalemia, particularly when renal insufficiency is present

Other adverse reactions to furosemide were reported infrequently Although furosemide causes an isotonic diuresis it can produce hyponatremia and/or hypochloremia Metabolic alkalosis hyperglycemia and hyperuricemia were attributed to furosemide in a few instances in this series, these effects have also been associated with ethacrynic acid and thiazide diuretics[3] Hearing loss has been reported after high dose parenteral furosemide[33] but no such cases were observed in our series

The present study suggests that furosemide is a relatively safe diuretic in a wide range of clinical situations The frequency of untoward effects in our series is comparable to that associated with the thiazides despite the greater diuretic effectiveness of furosemide Serious adverse reactions are quite uncommon, and occur primarily in the seriously ill Furosemide's efficacy and lack of serious clinical toxicity probably account for its widespread use

Summary

Of 17,068 hospitalized medical patients monitored in a drug surveillance program 2 367 (13 9 per cent) received furosemide Of these patients, 53 per cent were hospitalized with a primary (first) diagnosis of cardiovascular disease many other patients had cardiovascular disorders coincident with other diseases In 78 per cent of cases the indication for furosemide therapy was congestive heart failure Adverse reactions were attributed to furosemide in 239 patients (10 1 per cent) but in only 14 instances were the unwanted effects considered life threatening The most common adverse reactions were intravascular volume depletion (4 6 per cent of furosemide recipients), hypokalemia (3 6 per cent), and other electrolyte disturbances (1 5 per cent) Many patients experienced more than one manifestation of toxicity The over all frequency of adverse reactions increased progressively with higher daily doses of furosemide but was not correlated with total furosemide dose Among furosemide recipients who also received potassium supplements or potassium sparing diuretics hypokalemia was less frequent, less severe and of slower onset Coadministration of other diuretics with furosemide was associated with a higher frequency of volume depletion The findings indicate that furosemide is a relatively safe diuretic in a wide range of clinical situations Serious adverse reactions are uncommon and occur primarily in the seriously ill

Hospitals which have participated in the Boston Collaborative Drug Surveillance Program are Boston Mass—Lemuel Shattuck Hospital Peter Bent Brigham Hospital Boston City Hospital Boston Veterans Administration Hospital Massachusetts General Hospital and Boston University Hospital Providence R I—Roger Williams General Hospital Syracuse N Y—State University Hospital of the Upstate Medical Center Tucson Ariz—Arizona Medical Center Richmond Va—Virginia Commonwealth University Hospital Canada—St Joseph's Hospital London Ontario Israel—Hadassah-Hebrew University Hospital Jerusalem Beilinson Medical Center Petah Tiqva and Asaf Harofe Hospital Zerifin New Zealand—Auckland Hospital Auckland and Hutt Hospital Wellington Scotland—Western Infirmary and Stobhill General Hospital Glasgow Italy—Desio Hospital Milan

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furosemide It occurred in about 5 per cent of recipients, and was usually manifested as a rise in BUN The diuretic effectiveness of furosemide probably accounts for unintended volume depletion although increased venous capacitance[16] and decreased cardiac output[17] may contribute to hypotension in some patients Coadministration of other diuretics was associated with a higher frequency and possibly a greater extent of volume depletion

Clinically important hypokalemia was reported as an adverse reaction to furosemide in 4 2 per cent of recipients Coadministration of potassium supplements or potassium retaining diuretics did not completely prevent hypokalemia, but did appear to reduce its frequency and severity and to delay its onset This might be a spurious finding due to more intensive physician monitoring of the nonsupplemented patients but it is more likely that prophylactic potassium supplementation or coadministration of potassium sparing agents does in fact reduce the frequency and severity of diuretic induced hypokalemia However the widespread need for potassium supplementation during diuretic therapy is not established and it is unclear whether the benefits outweigh the risks Not all patients receiving diuretics experience depletion of total body potassium, and such depletion may be present without hypokalemia Furthermore administration of potassium chloride or spironolactone carries the risk of hyperkalemia particularly when renal insufficiency is present

Other adverse reactions to furosemide were reported infrequently Although furosemide causes an isotonic diuresis it can produce hyponatremia and/or hypochloremia Metabolic alkalosis hyperglycemia and hyperuricemia were attributed to furosemide in a few instances in this series these effects have also been associated with ethacrynic acid and thiazide diuretics Hearing loss has been reported after high dose parenteral furosemide[33] but no such cases were observed in our series

The present study suggests that furosemide is a relatively safe diuretic in a wide range of clinical situations The frequency of untoward effects in our series is comparable to that associated with the thiazides, despite the greater diuretic effectiveness of furosemide Serious adverse reactions are quite uncommon and occur primarily in the seriously ill Furosemide s efficacy and lack of serious clinical toxicity probably account for its widespread use

Summary

Of 17,068 hospitalized medical patients monitored in a drug surveillance program 2,367 (13 9 per cent) received furosemide Of these patients, 53 per cent were hospitalized with a primary (first) diagnosis of cardiovascular disease, many other patients had cardiovascular disorders coincident with other diseases In 78 per cent of cases the indication for furosemide therapy was congestive heart failure Adverse reactions were attributed to furosemide in 239 patients (10 1 per cent) but in only 14 instances were the unwanted effects considered life threatening The most common adverse reactions were intravascular volume depletion (4 6 per cent of furosemide recipients) hypokalemia (3 6 per cent) and other electrolyte disturbances (1 5 per cent) Many patients experienced more than one manifestation of toxicity The over all frequency of adverse reactions increased progressively with higher daily doses of furosemide but was not correlated with total furosemide dose Among furosemide recipients who also received potassium supplements or potassium sparing diuretics hypokalemia was less frequent, less severe and of slower onset Coadministration of other diuretics with furosemide was associated with a higher frequency of volume depletion The findings indicate that furosemide is a relatively safe diuretic in a wide range of clinical situations Serious adverse reactions are uncommon and occur primarily in the seriously ill

Hospitals which have participated in the Boston Collaborative Drug Surveillance Program are Boston Mass—Lemuel Shattuck Hospital Peter Bent Brigham Hospital Boston City Hospital Boston Veterans Administration Hospital Massachusetts General Hospital, and Boston University Hospital Providence R I—Roger Williams General Hospital Syracuse N Y—State University Hospital of the Upstate Medical Center Tucson Ariz—Arizona Medical Center Richmond Va—Virginia Commonwealth University Hospital Canada—St Joseph s Hospital London Ontario Israel—Hadassah-Hebrew University Hospital Jerusalem Beilinson Medical Center Petah Tiqva and Assaf Harofe Hospital Zerifin New Zealand—Auckland Hospital Auckland and Hutt Hospital Wellington Scotland—Western Infirmary and Stobhill General Hospital Glasgow Italy—Desio Hospital Milan

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Table I Diagnoses and clinical course in patients with ascending aorta-pulmonary artery anastomosis

Lesion	*No*	*Operative mortality*	*Late mortality*	*Mortality at repair*	*Alive*		
					Palliated	*Repair*	*Total*
Tetralogy of Fallot	106 (51%)	15 (14%)	7 (7%)	9	47	28	75 (71%)
With pulmonary stenosis	81 (39%)	11 (14%)	7 (9%)	7	31	25	56 (69%)
With pulmonary atresia	25 (12%)	4 (16%)	0	2	16	3	19 (76%)
Tricuspid atresia	24 (11.5%)	7 (9%)	0	–	17	–	17 (71%)
Pulmonary atresia With intact septum	27 (13%)	11 (41%)	7 (26%)	–	9	–	9 (33%)
Complex cyanotic congenital heart disease	51 (24 5%)	17 (33%)	7 (14%)	1	22	4	26 (51%)
Total	208	50 (24%)	21 (10%)	10 (5%)	95 (46%)	32 (15%)	127 (61%)

ment or associated with another palliative operation were classified as late Deaths resulting from intracardiac repair were grouped separately

The life of the shunt or follow up period was defined as the interval between creation of the APA and either another operation (reparative or palliative) death or last outpatient visit

Data on all infants with tetralogy of Fallot undergoing primary repair utilizing hypothermic circulatory arrest between 1973 and 1974 were obtained from the Department of Cardiovascular Surgery

Results

Diagnostic categories Two hundred and eight patients underwent APA at the Children s Hospital Medical Center Boston between 1965 and 1974 (Table I) Over 50 per cent of the operations were performed on patients with tetralogy of Fallot pulmonary atresia with intact ventricular septum and tricuspid atresia each were represented at 10 per cent of the total One quarter of the patients included a variety of complex cyanotic lesions such as double outlet right ventricle with pulmonary outflow tract obstruction single ventricle with pulmonic stenosis heterotaxy syndrome and transposition of the great arteries (D or L) with ventricular septal defect and pulmonic stenosis or atresia The median age of operation for all patients was three months for those with pulmonary atresia and intact ventricular septum four days for the complex group two months those with tricuspid atresia or tetralogy of Fallot with pulmonary atresia three months and for patients with tetralogy and pulmonary stenosis 10 months Eighty two of the 208 (39 per cent) operations were performed in patients one month of age or younger and two thirds were in the first year of life

Outcome of operation *Mortality* A summary of the clinical course in 208 patients is shown in Fig 1 The median follow up period after APA or shunt life as defined in methods was 13 months It may be seen that 50 patients died within one month after operation eight of these were intra operative deaths The cause of death was attributed to inadequate pulmonary blood flow in 14 heart failure in 12 moribund condition at the time of referral in eight sepsis in four arrhythmias in three and other factors in the remaining nine Twenty one additional patients died later but prior to repair at a median interval of six months after APA Of the 137 survivors (66 per cent) the majority are either awaiting surgical repair or are presently considered inoperable and 42 underwent repair with 10 deaths Thus 127 patients (61 per cent) are long term survivors

Mortality (prior to intracardiac repair) was related to age at APA There were 82 patients operated upon under one month of age with an over all mortality rate of 50 per cent (41/82) By contrast the mortality rate in patients one month and older was 24 per cent

The survival rate according to specific cardiac lesions is shown in Table I Almost three quarters of those with tetralogy of Fallot or tricuspid atresia are alive at latest follow up compared to only one third to one half of patients with pulmonary atresia and intact ventricular septum

Ascending aorta–pulmonary artery anastomosis for cyanotic congenital heart disease

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Aldo R Castaneda, M D
Boston Mass

Systemic to pulmonary artery anastomoses such as Blalock Taussig,[1] Potts and associates and Waterston,[3] were developed at a time when no other surgical treatment was available for infants and children with congenital heart disease resulting in a right to left shunt and inadequate pulmonary blood flow The early and late morbidity and mortality rates of each of these procedures has been critically reviewed in recent years [4-9] We have now moved into an era where alternative therapy employing early intracardiac repair, for some defects such as tetralogy of Fallot, is feasible [10]

This report reviews our experience with the ascending aorta pulmonary artery anastomosis (APA) in 208 patients and our recent results of primary repair in 16 infants with tetralogy of Fallot The mortality rate and consequences of APA and the alternative or primary intracardiac repair in infants with tetralogy of Fallot are evaluated

Methods and materials

The files in the Medical Records Departments and the Departments of Cardiology and Cardiovascular Surgery at the Children s Hospital Medical Center from 1965 to 1974 were searched for patients undergoing APA for cyanotic congenital heart disease Excluded were all patients with pulmonary artery to descending aorta anastomosis and those in whom a prosthetic conduit was used for anastomosis Included were all the anastomoses between the ascending aorta and the right pulmonary artery, and occasionally in patients with malposition of the great arteries, the left pulmonary artery The medical records, the electrocardiograms, as well as all data obtained at cardiac catheterization, operation, or autopsy were reviewed

Two thirds of the APA were performed in the first five year period (1965 1969) and one third in the last five years Severe hypoxemia with or without acidosis was the indication for surgery in all infants In the earlier years elective APA was also undertaken in a few older children with more modest hypoxia who needed additional palliation The majority of patients underwent preoperative cardiac catheterization and most operations up to 1973 were performed in the hyperbaric chamber The anastomosis was designed to be approximately 3 mm in internal diameter and was performed by one of four cardiac surgeons Narrowing and/or enlarging of initially inappropriate APA, performed at the initial operation based on clinical indications (presence or absence of a thrill high or low oxygen saturation) were not included as separate operative interventions

For purposes of analysis the patients were divided into several groups (Table I) Operative mortality was defined as death occurring at surgery during initial hospitalization or within the first month following operation Deaths occurring after this time during medical manage

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Table II Pulmonary vascular obstructive disease after ascending aorta-pulmonary artery anastomosis (APA)

Initials	*Diagnosis*	*Age at surgery*	*Age at catheterization (years)*	*Pulmonary artery pressure (mm Hg)*	*Pulmonary/systemic resistance (units)*
J O	Tetralogy	2 days	3 3/12	88/46	7 4/21 0
S C	Tetralogy	1 10/12 yr	3 10/12	62/32	5 1/16.2
P H	Dextrocardia corrected transposition with pulmonary atresia and ventricular septal defect	1 day	7 3/12	90/60	6 8/19 7
R F	Tetralogy	4 8/12 yr	12 8/12	90/63	6 0/15 0

Inadequate pulmonary blood flow after APA was the cause of death in 14 of 50 (28 per cent) early and seven of 21 (33 per cent) late deaths In the remainder of the patients with progressive hypoxemia additional palliative procedures or intracardiac repair was performed

Hemodynamics Eighty-eight patients underwent 97 cardiac catheterizations at a median time interval of 55 months following initial shunt surgery

Kinking of the pulmonary artery was detected on angiography in nine of 87 (10 per cent) but this did not prove to be a limiting factor in any who underwent subsequent repair The APA proved to be nonfunctioning in five patients Pulmonary atresia developed presumably due to an absence of mechanical stimulus to grow or even to remain patent when blood flow bypasses the pulmonary outflow tract in 8/39 patients (20 5 per cent) with tetralogy of Fallot during a mean interval of four years

Pulmonary artery hypertension (PAH) defined as a pulmonary artery systolic pressure greater than 40 mm Hg (range 40/25 to 100/40 mm Hg and > 75 systolic in one half) was noted in 12/72 (17 per cent) patients in whom the pulmonary artery was entered seven of these had heart failure early in their postoperative courses Catheterization in these patients was performed 1½ to 8 years after APA (median 6½ years) There was no relationship between the development of PAH and the age at which the operation was performed Pulmonary vascular obstructive (PVO) disease defined as a pulmonary arterial resistance > 5 units/M or > 1/3 systemic resistance levels was noted in four of the 12 patients with pulmonary artery hypertension or 6 per cent of survivors who underwent recatheterization (Table II) Three patients had a solitary APA shunt patient S C had two previous shunts as well as obstruction of the left pulmonary artery Two children (P H and R F) underwent intracardiac repair One (P H) with severe right sided heart failure survived but catheterization three months after repair documented persistent pulmonary vascular obstructive disease at the preoperative level The other R F died at operation and at postmortem pulmonary vascular obstructive disease was demonstrated The two other children are currently awaiting correction

Systemic arterial pulse pressure at catheterization was equal to or greater than 60 mm Hg in 12/53 equal to or greater than 70 mm Hg in 6 (11 3 per cent) and wider in only four Elevated left ventricular end diastolic pressure (defined as greater than 12 mm Hg before angiogram) was noted in 5/25 patients (20 per cent)

Cardiac catheterization following intracardiac repair and closure of APA was performed in eight patients The APA remained patent in four but the left to right shunt was minimal

Somatic growth in patients with tetralogy of Fallot was recorded for patients followed for a minimum period of one year after operation Patients over 13 years at last growth determination and those with Down s syndrome were excluded Adequate growth was present in 20/36 (56 per cent) while growth retardation (defined as a height and weight maturation at or below the third percentile) was present in 16/36 (44 per cent) children Heart failure was significantly present more frequently in those children with inadequate growth (7/16) as opposed to those in whom growth was adequate (0/20) On the other hand the frequency of hypoxemia was not different (6/16 versus 5/20) between the two groups

Bacterial endocarditis occurred in 3 (1 4 per

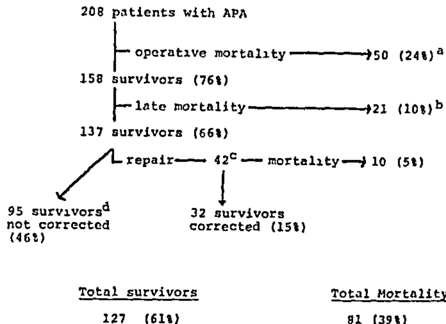


Fig 1 Prognosis of 208 patients undergoing ascending aorta pulmonary artery anastomosis (APA) Percentages based on initial 208 patients Additional palliative procedures performed in 26 patients of group a 12 patients in group b 17 patients in group c and 35 patients in group d

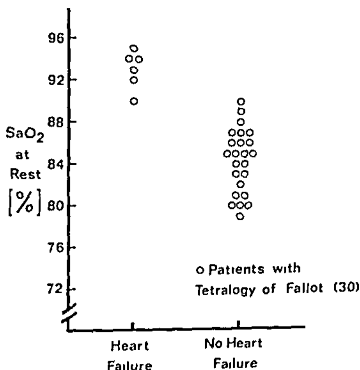


Fig 2 Systemic arterial oxygen saturation (SaO) determined by ear oximeter at discharge from hospital in 30 patients with tetralogy of Fallot following ascending aorta pulmonary artery anastomosis Infants with $SaO_2 \geq 90$ per cent nearly always had heart failure

or other complex cyanotic lesions Median follow up period for patients with pulmonary atresia and intact ventricular septum was two months, for those with tricuspid atresia 11 months for patients with complex cyanotic heart disease 17 months, 26 months in patients with tetralogy with pulmonic stenosis and 38 months in patients with tetralogy with pulmonary atresia

Systemic arterial oxygen saturations The ear oximeter is an easily available practical tool in following the progress of patients with APA and the values obtained correlate well with arterial oxygen saturation determined by reflection oximeter[11] Oxygen saturations at last encounter in 91 patients ranged from 55 to 94 per cent (mean 84 per cent) Fig 2 depicts the relationship between systemic arterial oxygen saturations and congestive heart failure in patients with tetralogy of Fallot and indicates that postoperative saturations of 90 per cent or greater are associated with congestive heart failure The ideal resting oxygen saturation in the postoperative patients with APA shunt might be in the low to mid 80 s

Roentgenograms Definite cardiomegaly on chest x ray was present in 74/110 (67 per cent) and increased pulmonary flow pattern was noted in 52/110 (47 per cent) at the last examination prior to intracardiac repair or additional palliation

Congestive heart failure occurred in 53 of the entire group of 208 patients (25 5 per cent) 37 per cent (30/82) of infants less than one month of age and 18 per cent (23/126) of those beyond this age Heart failure was responsible for 12 of 50 early (24 per cent) and 3 of 21 (14 per cent) late deaths A pattern of right sided massive pulmonary flow and pulmonary edema was noted in the early postoperative period in 12 patients of these 9 (75 per cent) died The mortality rate in all patients with congestive heart failure was 43 per cent (23/53)

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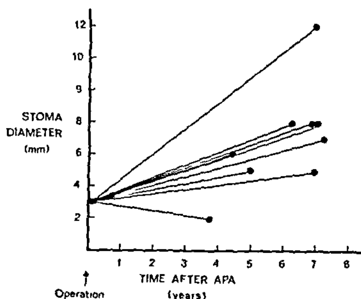


Fig 3 Growth in orifice size of ascending aorta pulmonary artery anastomosis (APA) Initial diameter of 3 mm increased with time in all but one patient

cent) patients—two were clinically diagnosed and successfully treated and one was found at post mortem examination

Anastomosis orifice size In 13 patients who died within one month after surgery, measurement of the orifice size was performed at postmortem In all six patients with severe postoperative hypoxemia the diameter of the orifice was less than 2 mm In the seven patients who died with congestive heart failure the diameter of the anastomosis was 2 to 5 5 mm (mean 3 mm) Among four patients who died longer than a month postoperatively with inadequate pulmonary blood flow the anastomosis was obliterated in three in one of these closure was by bacterial vegetation In the remaining one it was patent and measured 3 mm in diameter The orifice size of the anastomosis was measured in nine patients during intracardiac repair and was compared to the measurement (3 mm) at initial creation the stoma had greatly enlarged in diameter in all but one (Fig 3)

Additional palliative surgery A total of 118 additional palliative procedures were performed at 99 operations in 90 patients These additional procedures were performed prior to the APA in 20 per cent (42/208) during the same operation in 6 per cent (12/208) and after the APA in 14 per cent (28/208) (Fig 1) The procedures included 44 Blalock Taussig operations 23 Brock type pulmonary valvotomies 18 APA narrowings 10 atrial septal defect creations nine Potts shunts and other less frequently performed procedures (Glenn operation, central shunt usually employing a prosthesis a second APA, or enlarging of an APA)

Seventeen patients (8 per cent) underwent operations to narrow the shunt by means of external constriction because of unrelenting congestive heart failure or pulmonary edema The narrowing was performed within 24 hours after APA in 12 patients six of these died within a few days after surgery Five patients underwent narrowing of the APA between five months to three years (median eight months) after initial APA One died during operation and four are alive Total mortality rate for shunt narrowing was 41 per cent 50 per cent (6/12) when performed within the first 24 hours and 20 per cent (1/5) when performed later

Primary versus two staged repair in tetralogy of Fallot in infancy To address ourselves to a presently lively controversy we have compared the total mortality rate of patients with tetralogy

Table III Surgical results of primary and staged repair in infants under one year of age with tetralogy of Fallot (excluding pulmonary atresia)

Procedure	Number of patients	Age mean (range)	Mortality No	Mortality (%)
Two stage repair (1965 1974)				
Ascending aorta to pulmonary artery shunt	35	3 mo (1 day 10 mo)	10	(29)
Repair	9		1	(11)
Awaiting repair	16			
Primary repair (1973 1974)	16	4 mo (12 days 10 mo)	1	(6)

Table IV Complications of ascending aorta-pulmonary artery anastomosis

Congestive heart failure
Unilateral pulmonary edema
Obliteration of shunt
Pulmonary artery hypertension
Pulmonary vascular obstructive disease
Kinking of right pulmonary artery
Hypoxia inadequate shunt
Residual patency after repair
Growth of stoma with time
Stenosis of right pulmonary artery after repair
Endocarditis

of Fallot who were subjected first to an APA shunt within the first year of life and later repair and sixteen consecutive infants undergoing pri mary repair utilizing hypothermia circulatory arrest within the last two years Table III summarizes our results and indicates that in this small group of patients and being cognizant of the inherent problems with retrospective studies particularly comparing two different time peri ods the primary repair is superior to the two stage approach

Comments

The APA has been shown to be an effective palliative procedure for nearly 13 years The operation is most useful in young infants with cyanotic congenital heart disease in whom the anatomy is not favorable either for primary repair or for a subclavian artery–pulmonary artery anastomosis The various types of palliative procedures their indications relative advantages modifications and complications have been previously reviewed [14] Complications of APA are seen in Table IV Heart failure is one of the most common adverse consequences[10, 15-1] despite efforts to create an anastomosis that is small enough to prevent excess pulmonary flow Neo nates as this study shows are particularly prone to this complication partially because of a fall in the initially increased pulmonary resistance and partially on account of the growth of the stoma that might have been initially ideal in size In many cases failure can be controlled by digitalis and diuretics—but occasionally when the shunt produces unrelenting heart failure a further surgical intervention is necessary Since narrow ing of the anastomosis in our experience has a high mortality rate we recommend repair If this is not feasible replacement with another shunt is preferable to attempt to manipulate the APA

Pulmonary artery hypertension was docu mented on serial cardiac catheterization in 17 per cent and a third of these had appreciable PVO This is not an unexpected finding in patients with a large shunt and increased pulmonary blood flow present for many years Given the same stoma diameter and duration of shunt patency we would expect the incidence of these complications to be the same in patients with APA as it is in those with a Potts shunt It is of interest that two of our patients developed significant PVO within four years after APA Therefore we would recommend routine recatheterization of patients with APA within two years after the procedure By that time infants with many lesions may be suitable candidates for repair

The mortality rate for APA in our institution as well as others[7, 2, 15, 20, 21] is high Because of the great variation in the type and age of populations and the manner in which data are collected and presented comparisons between different institu tions are very difficult Most deaths however are intraoperative or within one month of initial hospitalization The mortality is related to the complexity of the cardiac lesions accuracy of preoperative diagnosis the severity of hypoxia or acidosis prior to surgery age at operation skill of the surgeon and adequacy of postoperative man agement

Early results of primary repair in babies with tetralogy of Fallot at our institution (Table III) have been so promising that for the majority we would now recommend this procedure in prefer ence to palliation only those with pulmonary atresia abnormal coronary artery distribution or very small pulmonary arteries are palliated On the other hand for infants under six months of age with complex forms of cyanotic heart disease and those with tetralogy who are not candidates for repair APA is the procedure of choice Within this group those with tetralogy with pulmonary atresia and those with tricuspid atresia undergo APA with an aceptable mortality rate However patients with pulmonary atresia with infant ventricular septum have an extremely high oper ative and late mortality rate We have not exper ienced the technical difficulties especially those related to kinking interruption of continuity between right and left pulmonary arteries and obliteration of the right pulmonary artery described by others in the removal of the APA at intracardiac repair[7, 2, 7] However patency of the shunt after attempted closure has been docu mented in four of eight patients

Summary

The course and prognosis of 208 patients with an ascending aorta to pulmonary artery anasto mosis is reviewed Mortality rate during or within one month of surgery was 24 per cent (50/208) and late mortality rate prior to repair was 10 per cent (21/208) An additional 5 per cent (10/208) died during subsequent intracardiac repair Con gestive heart failure developed in 25 per cent (53/

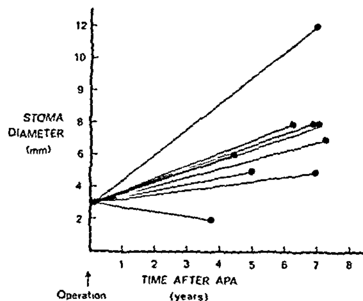


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Accelerated atrioventricular conduction during acute myocardial infarction

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Timisoara Romania

Accelerated atrioventricular (A V) conduction manifesting as Wolff Parkinson White syndrome or as a short PR interval with normal QRS complex has been occasionally reported in association with acute myocardial infarction [1]

Three patients showing this association have been observed and studied in order to explain the mechanism by which this phenomenon may occur

Case reports

Case 1 An 82 year old woman with a ten year history of angina pectoris was hospitalized with acute pulmonary edema An electrocardiogram taken three months before showed nonspecific ST T changes (Fig 1*A*) on admission it revealed an inferior wall myocardial infarction (Fig 1*B*) the PR interval measured 180 msec and QRS duration was 60 msec Serum glutamic oxalacetic transaminase was 125 units blood glucose was 1/0 mg per cent other laboratory data were nonrelevant On the second hospital day a delta wave was visible in Leads I and II the PR interval was 100 msec and QRS duration measured 90 msec (Fig 1*C*) The patient s status improved under treatment with bed rest digitalis and diuretics Ten days after the admission an His bundle electrogram was recorded with a tripolar electrode catheter introduced via the right femoral vein A second bipolar pacing electrode was introduced through the right mediobasilic vein into the right atrium A specially constructed battery powered impulse generator was used for pacing the heart All recordings were obtained with a six channel direct writing electrocardiograph (NEK 6-Zwonitz, East Germany) at a paper speed of 50 or 100 mm /second The H V intervals were measured from the spike of H deflection to the earliest ventricular recording in any surface lead (at least two leads in which the delta wave was most evident) This procedure was also used in the others studied cases On the His bundle recording an A H interval of 50 msec and an H V interval of 35 msec were measured during sinus rhythm Scanning of the cardiac cycle with an atrial stimulus approximately twice diastolic threshold during sinus rhythm was then performed Stimuli falling at 240 to 260 msec from the beginning of atrial depolarization were conducted to the ventricular with a stimulus *to R* interval of 280 to 300 msec and a narrow QRS complex (Fig 2*B* and *C*) while those falling at 300 msec or more were conducted with the preexcitation pattern (Fig 2*A*) The beats with a narrow QRS complex had a frontal axis shifted upward and to the left Such beats were conducted to the *ventricle with A H and H V* intervals of 160 and 80 msec respectively the latter value suggesting latent conduction disturbance in the His Purkinje *system (Fig 2C)*

The patient recovered and was discharged after three weeks of hospital stay She complained of shortness of breath and angina pectoris Her electrocardiogram remained unchanged showing the WPW pattern After four months she developed suddenly crushing chest pain followed by acute pulmonary *edema.* She was admitted in a state of profound shock and died on the following day

On autopsy a recent infarction involving the anterolateral wall of the left ventricle and the

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208) pulmonary artery hypertension in 17 per cent (12/72), and pulmonary vascular obstruction in 6 per cent (4/72) An increase in orifice size of the stoma with time was documented in eight patients Additional subsequent palliative surgery was required in 22 per cent (45/208) Mortality rate was directly related to age at operation and was highest in neonates less than one week of age In infants with tetralogy of Fallot, a preliminary comparison of mortality rate between palliative surgery and primary repair clearly suggests that the latter is the preferred method of treatment

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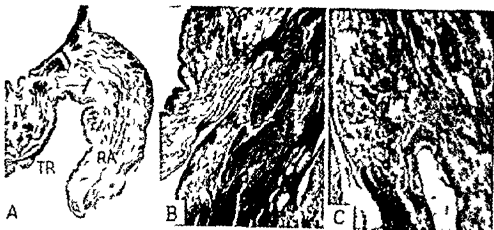


Fig 3 Case 1 *A* Accessory atrioventricular tract (*arrow*) making the connection between the right atrial wall (*RA*) and the insertion of the posterior leaflet of the tricuspid valve (*TR*) *B* The arrow points the connection between the fascicle shown in *A* and the interventricular septum (*IV*) *C* Muscular fibers passing from the outer to the inner aspect of the insertion of the posterior leaflet of the tricuspid valve (Hematoxylin and eosin Original magnification *A* × 12 *B* × 160 *C* × 300)

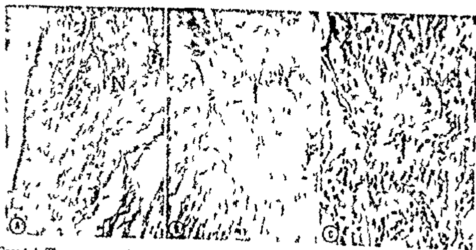


Fig 4 Case 1 *A* The compact node area (*N*) *B* and *C* Arrows showing foci of necrosis. (Hematoxylin and eosin Original magnification *A* × 200 *B* × 300 *C* × 360)

conducting system showed nonspecific degenerative changes due probably to ischemia and old age No attacks of supraventricular tachycardia were noted during the presence of the WPW pattern

Case 2 A 47 year old man was admitted to the hospital with acute precordial pain His past history was noncontributory On admission the electrocardiogram showed an anterior wall myocardial infarction The PR interval was 180 msec QRS duration was 80 msec and heart rate was 125 beats per minute (Fig 5*A*) Serum glutamic oxalacetic transaminase was 200 units The next day a shortening of the PR interval to 100 msec (Fig 5*B*) and frequent atrial premature beats with atrial echoes were noted (Fig 6*A*) A His bundle recording performed at this time (Fig 6*B*) showed a short A H interval (30 msec) and a normal H V interval (50 msec) With atrial pacing up to a rate of 130 per minute the A H interval lengthened to 90 msec (Fig 6*C*) This procedure was done to validate the H deflection On the third hospital day a paroxysm of tachycardia with a rate of 187 per minute occurred (Fig 7*A*) A second His bundle recording during the attack of rapid heart action showed that each ventricular complex was preceded by an atrial depolarization and an H deflection (Fig 7*B*) During the arrhythmia the A H interval was 150 msec while the H V interval remained unchanged (50 msec) No retrograde H deflection could be observed During the ectopic rhythm the

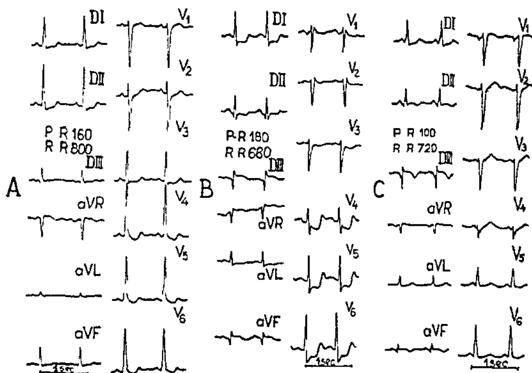


Fig 1 Case 1 *A* Electrocardiogram taken three months before *B* Electrocardiogram on admission showing inferior wall infarction *C* Electrocardiogram on the second hospital day showing preexcitation pattern

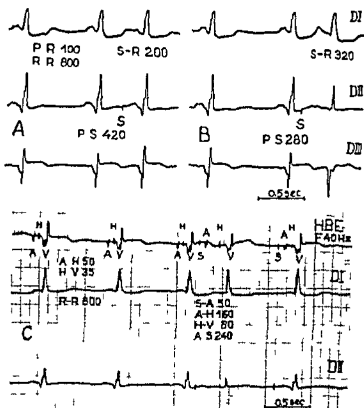


Fig 2 Case 1 Upper panels (*A and B*) show electrocardiogram taken during the scanning of the cardiac cycle with atrial electrostimuli during sinus rhythm A stimulus falling at 420 msec from the beginning of the P wave is conducted to the ventricles with the preexcitation pattern (*A*) while a stimulus falling at 280 msec is conducted with a narrow QRS complex and a leftward axis deviation (*B*) Lower panel (*C*) shows His bundle electrogram (*HBE*) recorded simultaneously with Leads I and II A H, and V are atrial His bundle and ventricular activity

interventricular septum was found There was also an old infarction of the inferior wall and of the apex with aneurysmal dilatation and parietal thrombosis Extensive atherosclerosis of the aorta and coronary arteries was present

The A V conduction system was studied according to Davies[7] the right and left A V rings were also included in the histologic study the sections being made perpendicularly to the A V ring A well marked atrioventricular tract was found on the posterior wall of the right atrium It passed superficially to the A V node and ended at the level of the insertion of the posterior tricuspidal leaflet (Fig 3*A*) At this level fibers of the accessory tract entered into the upper interventricular septum (Fig 3*B*) No other abnormal A V connections could be found In the A V conduction system there was a moderate degree of fibrosis, scattered foci of necrosis in the compact node area (Fig 4) and leucocytic infiltrates within the bundle of His and its branches

The atrial and ventricular myocardium showed pronounced hypertrophy of cardiac muscle fibers there were hemorrhages and vascular stasis around the corpus fibrosus

To summarize this patient developed during an acute myocardial infarction a WPW pattern suggesting right posterior preexcitation[7] On autopsy an accessory bundle was found on the posterior edge of the right A V ring The A V



Fig 3 Case 1 *A* Accessory atrioventricular tract (*arrow*) making the connection between the right atrial wall (*RA*) and the insertion of the posterior leaflet of the tricuspid valve (*TR*) *B* The arrow points the connection between the fascicle shown in *A* and the interventricular septum (*IV*) *C* Muscular fibers passing from the outer to the inner aspect of the insertion of the posterior leaflet of the tricuspid valve (Hematoxylin and eosin Original magnification *A* × 1., *B* × 160 *C* × 300)



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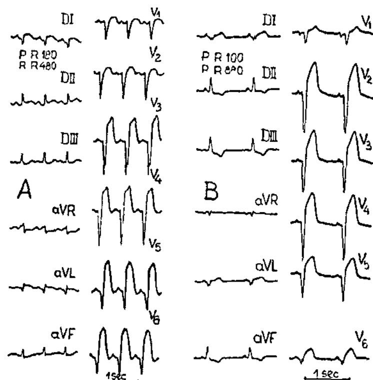


Fig 5 Case 2 *A* Electrocardiogram on admission *B* Electrocardiogram on the second hospital day showing short P R interval

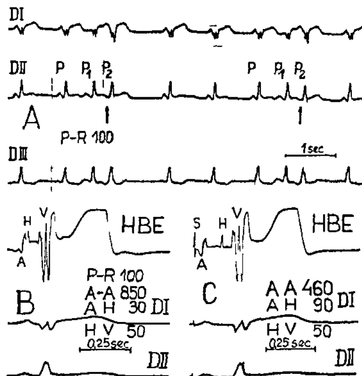


Fig 6 Case 2 *A* Electrocardiogram showing atrial premature beats (P) and echo beats (P) The arrows point to retrograde P wave which precedes the QRS complexes of the echo beats *B* His Bundle electrogram (*HBE*) showing short A H interval *C* Atrial pacing at a rate of 130 per minute resulted in a lengthening of the A H interval from 30 to 90 msec

patient developed severe precordial pain and hypotension DC shock stopped the attack but it recurred after two hours and was successfully

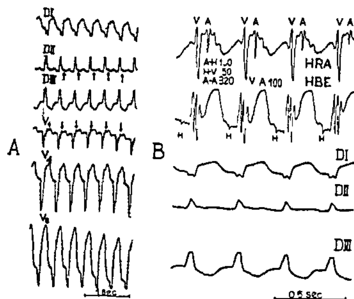


Fig 7 Case 2 Electrocardiogram (*A*) and His bundle electrogram (*B*) recorded during tachycardia *HRA* = high right atrial electrogram

controlled with digoxin The subsequent course was uneventful The electrocardiographic configuration with short PR interval remained unchanged during a follow up period of 20 months and the patient had no attacks of tachycardia ever since

Case 3 *A 74 year old man with diabetes* mellitus and a five year history of angina pectoris was admitted with an acute inferoposterolateral myocardial infarction He showed signs and symptoms of congestive failure and an apical systolic murmur suggesting papillary muscle dysfunction During the first two weeks the PR *interval was 160 msec (Fig 8A) The patient* improved markedly under treatment with digitalis and diuretics However in the third hospital week his status worsened He presented frequent anginal episodes without any obvious reason During this period which lasted several days a short PR interval and frequent ventricular ectopic beats with retrograde conducted P waves were noted (Fig 8*C*) A His bundle recording showed an A H interval of 30 msec and an H V interval of 40 msec (Fig 9*A*) With atrial pacing up to a rate of 120 per minute the A H interval lengthened to 80 msec Short bouts of supraventricular tachycardia which stopped spontaneously were also observed The patient was discharged after six weeks of hospital stay After four months the electrocardiogram showed a normal PR interval (150 msec) while on the His bundle recording the following intervals were measured P A 60

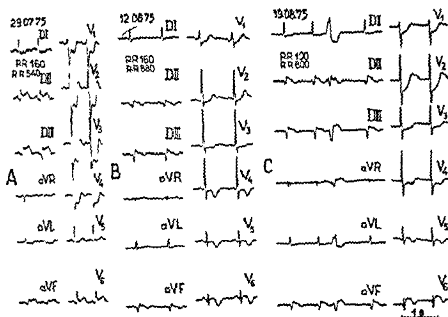


Fig 8 Case 3 Electrocardiogram recorded on admission (A) after two weeks (B) and after one week (C) when shortening of P R interval took place

msec A H 50 msec and H V 40 msec The patient remained in congestive failure but had no arrhythmic episodes

Discussion

The reported cases are examples of the so called acquired variety of the preexcitation syndrome It is now accepted that the WPW syndrome is due to abnormal atrioventricular connections Anatomic studies were able to demonstrate accessory muscular bridges between the atria and ventricles in apparently normal hearts It is possible that under particular influences such accessory bundles may become functional and conduct the cardiac impulse Levine and Burge reported a patient with an acute myocardial infarction and a high degree A V block in whom occasionally conducted beats showed the WPW pattern Goel and Han described two cases of the WPW syndrome appearing after the development of an acute myocardial infarction The electrocardiographic configuration of the myocardial infarction disappeared completely with the occurrence of preexcitation Supraventricular tachycardia occurred in both patients The WPW pattern disappeared with the recovery from the acute phase It was assumed that under the influence of increased autonomic nervous activity associated with acute

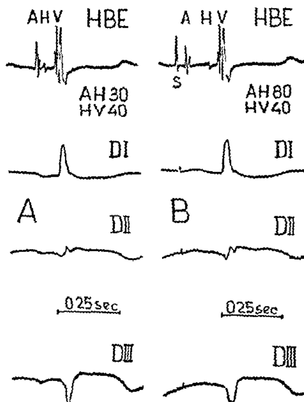


Fig 9 Case 3 A His bundle electrogram showing an A H interval of 30 msec corresponding to the electrocardiogram shown in Fig 8C B During atrial pacing at a rate of 120 per minute the A H interval lengthened to 80 msec This procedure was used to validate the H deflection

ischemia an aberrant A V bundle became functional[5] This hypothesis is supported by the observation that the preexcitation pattern could be elicited in a patient with intermittent WPW syndrome by concomitant isoprenaline infusion and carotid sinus massage[12]

In Case 1 the WPW pattern appeared during the first myocardial infarction and persisted for four months until the death due to a second infarction Nonspecific degenerative changes were present in the A V conduction system especially in the compact nodal area It is possible that these changes favored A V conduction through the accessory bundle No attacks of supraventricular tachycardia occurred, nor could be initiated during the scanning of the cardiac cycle with electric stimuli suggesting that no reentry circuit could be initiated This may be due to the pathologic changes within the A V conducting system However, stimuli falling at 240 to 280 msec from the beginning of atrial depolarization were conducted through the normal A V conduction system, with a prolonged H V interval and ventricular aberrancy There was a slight increase in the QRS duration from 60 to 90 msec associated with the appearance of the WPW configuration suggesting that A V conduction occurred over both normal pathways and also through the abnormal connection Although the preexcitation syndrome in this patient appears as acquired it could not to be excluded that during its life this pattern was present in other occasions

The anatomic study showed a correspondence between the electrocardiographic configuration suggesting right posterior preexcitation[7] and the localization of the accessory bundle The hypothesis of mismatch impedance,[11] which assumes an adequate relation between cable capacity of the conducting structure and the muscle mass which is to be activated may explain the preferential utilization of the pathway by which the cardiac impulse is conducted Autonomic nervous influences[5, 12] as well as pathologic changes in the A V conducting system can dissipate the mismatch impedance enhancing conduction over the accessory bundle

The appearance of the short PR interval associated with normal duration of the QRS complexes[14] during the course of acute myocardial infarction is more difficult to explain Although this phenomenon is said to be a rare event[4, 15] it was noted with variable frequency when large series of patients with myocardial infarction were studied[16, 17] The short PR intervals were noted especially on the first days of the illness, subsequently the tracings revealed normal PR intervals except in a few instances in which it remained unchanged for months[16] No mention is made about the associations with supraventricular tachycardia In our Cases 2 and 3 both developed attacks of rapid heart action shortly after the appearance of the preexcitation pattern This phenomenon was associated with atrial premature beats and atrial echoes in Case 2 and ventricular extrasystoles with retrograde activation of the atria in Case 3 Anginal pain was also a feature of the clinical picture No arrhythmic episodes were encountered in both patients nor in the past history and the follow up period In the absence of anatomic studies the mechanism of the shortening of the PR interval remains speculative It was suggested[7, 18] that shortening of the PR interval may be due to abnormal connections of the atriofascicular bypass type,[9] or to a particular pacemaker location and pattern of atrial activation[15] The demonstration of shortened refractory periods of the A V conducting system in patients with short PR intervals and normal QRS complexes was considered compatible with a partial A V nodal bypass or dual A V conduction but could not differentiate between these two possibilities[19] In Case 2 an A H interval of 30 msec was measured on the His bundle recording during sinus rhythm while during supraventricular tachycardia it was 150 msec This phenomenon can be explained by prolongation of the A H time with increased atrial rate or by the fact that during ectopic rhythm an accessory pathway was active[9] During supraventricular tachycardia no retrograde H′ deflections were recorded however, this does not exclude the possibility that ventriculoatrial conduction occurred via the abnormal connection (Fig 7) The H V interval was unchanged in sinus and ectopic rhythm

There is no firm evidence that accelerated A V conduction can be acquired during acute myocardial infarction However latent accessory A V connections may become functional under the complex changes due to acute myocardial ischemia and show various electrocardiographic patterns of preexcitation syndrome

Summary

Three cases are described in which accelerated atrioventricular conduction occurred during an acute myocardial infarction The first patient an

82 year old woman developed a WPW syndrome suggesting posterior right ventricular preexcitation a pattern which persisted for four months until her death An accessory bundle was found on autopsy Fibrotic changes associated with acute lesions (hemorrhage polymorphonuclear infiltrates) were present in the atrioventricular node and His Purkinje system

Two men of 47 and 74 years developed a short PR interval associated with supraventricular tachycardia during the course of an acute myocardial infarction The PR interval returned to its initial value in one case and remained unchanged for three months in the other

Accessory atrioventricular connections which became functional during myocardial ischemia may explain the various electrocardiographic patterns of preexcitation

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Summary

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LV and then withdrawn into the aortic root 1 to 2 cm above the valve Pressures were recorded simultaneously from LV and aorta using Statham strain gauges and an oscilloscopic recorder Because of its high frequency response the Statham P23Gb gauge was used for recording the LV pulse The LV dP/dt was obtained using a *resistance-capacitance differentiating circuit* (time constant 1.1 msec) connected to the output of the pressure channel The maximum error of the differentiator is approximately 0.9 per cent when summing the fundamental with the tenth *harmonic*[8] *Knopp Rahimtoola* and Swan[1] have demonstrated that conventional catheter systems and a circuit of this type provide a satisfactory method for recording the derivative within the physiologic range of man

The LV ejection fraction was measured by indicator dilution Indocyanine green dye* was introduced into the LV by sudden injection and blood was sampled at a rate of 2.0 ml /sec through the aortic catheter and a Gilford densitometer by means of a Harvard withdrawal pump The sampling dead space ranged from 1.0 to 1.5 ml and the 90 per cent response time for the catheter-densitometer system was approximately 0.6 sec For these curves concentration was plotted semilogarithmically as a function of stroke number Except for the initial one or two beats on some curves concentrations uniformly fell on a single slope of exponential decay From this slope the ejection fraction which is the ratio of stroke volume to end diastolic volume was calculated The *results* of two or more measurements of ejection fraction were averaged in each subject

Left ventricular ejection fraction by this technique has shown excellent reproducibility in a hydraulic model under nearly ideal conditions of mixing and sampling with a mean coefficient of variation of 3 per cent In vivo studies in the dog compared favorably the coefficient of variation being 6 per cent Although an absolute test of accuracy in vivo is not available three studies comparing the indicator dilution technique with quantitative angiocardiography have shown good agreement The study by Swan and associates represents a revision of a previous conclusion that indicator dilution data differ substantially from those by angiography Finally *recent* studies from our laboratory have shown that adequate mixing of injected dye with LV blood *occurs if injection is made into either the apex of* the LV as in the present study or the inflow tract[16]

Cardiac output except in patients with atrial septal defect was measured from indocyanine *green dilution curves sampled from the aortic* root after pulmonary artery or right atrial injection For these curves concentration was plotted semilogarithmically as a function of time and extrapolated to 1 per cent of peak concentration Areas were obtained by summation of the concentrations and forward flow was calculated by the method of Kinsman Moore and Hamilton[17] Mean stroke volume was obtained as the average from two or more such curves In patients with atrial septal defect LV stroke volume was obtained from aortic dilution curves during continuous infusions of dye into the LV This technique has been shown to yield accurate measurements of minute flow[1] End diastolic volume was calculated as the ratio of mean stroke volume to mean ejection fraction

The dilution curves pressures LV dP/dt and ECG were recorded on an Electronics for Medicine DR 8 recorder LV stroke work (SW) in Gm M /beat/M[2] was calculated from the formula

$$SW = \frac{(SV)\ (LVMSP\ LVEDP)\ (1.36)}{100}$$

where SV = stroke volume in ml /M[2] $LVMSP$ = LV mean systolic pressure during ejection in mm Hg $LVEDP$ = LV end diastolic *pressure in mm Hg and 1.36* is the Hg correction factor The LV radius was calculated from EDV assuming a spherical ventricle at the end of the isovolumetric period and circumferential fiber length was calculated as 2πR Afterload was *calculated* as *mean* systolic tension during ejection from the LaPlace relation $T = KP_{T}R$ where P = mean systolic pressure during ejection in mm Hg R = mean systolic radius during ejection in cm and K = the constant (1333 dyes/cm /mm Hg) *converting the units to dynes*

Contractility was assessed in several ways Assuming a uniform series elastic constant but omitting a value for this constant from calculation (since all such values have been derived from animal or isolated heart muscle *studies)* the velocity of the contractile element (Vce) at peak dP/dt was calculated as the ratio of dP/dt max in mm Hg/sec to simultaneous LV pressure in mm

*Cardio-Green Hynson, Westcott and Dunning Inc

The state of the left ventricular myocardium in mitral stenosis*

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A classical physiologic hallmark of mitral stenosis is reduction in cardiac output due to subnormal stroke volume Some have attributed this low stroke volume to a defect in the left ventricular myocardium [1-4] However previous work from our laboratory has shown that the contractile state of the left ventricle in mitral stenosis is normal as are the coronary blood flow and oxidative metabolism, and we have attributed the low stroke volume in mitral stenosis to diminished pulmonary venous return to that chamber [5,6] Nevertheless reports continue to appear concluding on the basis of newer techniques for assessing cardiac muscle mechanics, that the left ventricular myocardium is abnormal in mitral stenosis [7-9]

To clarify this problem we have compared LV pump function contractile state and relaxation in mitral stenosis with the same variables in normal subjects and in two contrasting patient groups alcoholic cardiomyopathy, representing pathology confined to the myocardium, and atrial septal defect representing a hemodynamic lesion with right ventricular overload as in mitral stenosis but with no demonstrated or posited left ventricular pathology

Materials and methods

Twenty three patients and 10 normal subjects were studied by right and left heart catheterization in the basal postabsorptive state under mild barbiturate sedation and local procaine analgesia Clinically essential medications including digitalis in five of the patients with mitral stenosis were not discontinued The normal subjects were expected and found to be hemodynamically normal at catheterization Five had idiopathic dilatations of the pulmonary artery Three had chest pains considered nonanginal with negative ECG stress tests but disturbing family histories of precocious lethal vascular disease Two had vibratory systolic murmurs which had led to restriction from competitive athletics The 10 patients with mitral disease had pure stenosis and no other valvular lesion Six patients had atrial septal defect all of the ostium secundum type There were seven patients with cardiomyopathy all with a history of moderately heavy chronic ethanolism These cardiomyopathy patients were selected from a larger group with this lesion to provide a subgroup with myocardial pathology but like MS and ASD with normal left ventricular preload and afterload

Catheters were placed in the main pulmonary artery LV apex and aortic root The LV was entered by retrograde catheterization via the right brachial artery (6F 7F NIH catheters 80 cm long) The aortic catheter was polyethylene tubing (i d 1 13 mm 70 cm long) introduced through the left brachial artery by the Stille–Seldinger technique Its tip was advanced into the

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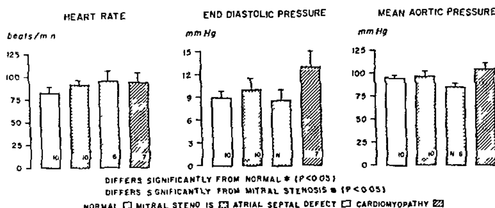


Fig 1 Heart rate left ventricular end diastolic and mean aortic pressures in normals and cardiac patients

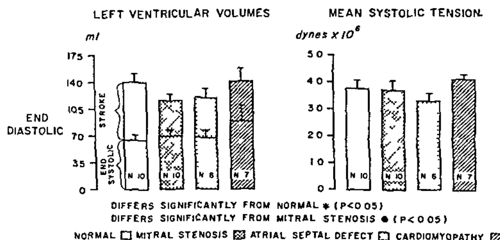


Fig 2 The left ventricular volumes and mean systolic tension (afterload) in the normals and three patient groups

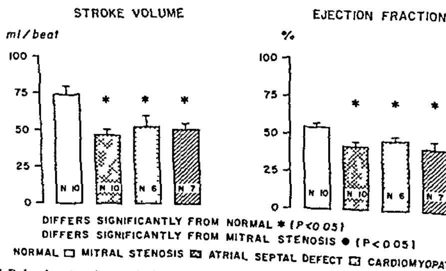


Fig 3 Reduced stroke volume and left ventricular ejection fraction indicate a decreased pump function in three patient groups

Table I Hemodynamics in patients with mitral stenosis

Patient	Age	Sex	Rhythm	PaSp*	PaDP	PaMP	MVG	MVA	CyIx	RIx
W M	32	M	RSR*	48	27	40	19	1 1	1 32	2 23
C M	51	M	AF	96	48	65	25	0 3	1 41	1 70
E S	29	F	RSR	42	20	30	13	1 1	1 13	3 72
C McV	59	F	AF	55	30	38	28	0 4	1 40	2 20
J D	40	M	AF	38	19	26	14	1 0	1 23	1 85
R C	27	F	RSR	32	18	25	21	0 7	1 12	2 58
F H	32	M	RSR	105	51	71	25	0 6	1 05	1 43
J S	40	M	RSR	44	18	31	9	1 3	1 23	1 53
M N	32	F	RSR	49	23	32	15	1 0	1 45	2 97
D F	53	F	RSR	42	23	31	20	0 6	1 33	2 59
Mean	39 5			55	28	38	19	0 8	1 26	2 28
SE ±	3 5			7 8	3 8	4 6	1 9	0 1	04	0 2

Abbreviations RSR = regular sinus rhythm AF = atrial fibrillation PaSP PaDP PaMP = pulmonary artery systolic diastolic and mean pressures respectively in mm Hg MVG = mitral valve gradient in mm Hg MVA = mitral valve area in cm SE = standard error CyIx = contractility index RIx = index of isovolumic relaxation

Hg, in accordance with Levine and Brittman [19] If the value for the elastic stiffness constant is taken as unity, then the units are muscle lengths per second In addition, contractility was obtained as the index of Frank and Levinson[6] which expresses the end isovolumetric velocity-force relation normalized for initial fiber length The index is calculated by the formula (dP/dt max/MIP)/ 2πR where MIP is the maximum isovolumetric pressure in mm Hg 2πR is the LV end diastolic circumference in cm, the ratio of dP/dt max to MIP (which are nearly simultaneous) [0] approximates Vce at peak dP/dt and at peak MIP, and the units of contractility are muscle lengths (ML) per second per cm of end diastolic circumferential fiber length

The state of the left ventricular myocardium was further explored in terms of its relaxation properties Several methods for describing this phase of the cardiac cycle were used Peak negative dP/dt, which always occurs during isovolumic relaxation has been reported to be a reproducible index of the rate of relaxation [1] However since it has been shown to be affected by contractility end systolic volume and afterload [1] isovolumic relaxation was characterized in this study by three indices (1) the ratio of peak negative dP/dt to peak positive dP/dt as described by McLaurin and colleagues [2] (2) peak negative dP/dt normalized for simultaneous pressure and termed the velocity of isovolumic relaxation (VIR) and (3) the VIR normalized further for circumferential fiber length termed relaxation index (RIx) [1] and calculated by the formula (peak dP/dt neg)/P/2πRes) where peak dP/dt negative is the maximum rate of LV pressure fall in mm Hg/sec, P is the pressure in mm Hg at peak dP/dt negative, 2πRes is the end systolic LV circumference in cm and the units are muscle lengths (ML) per second per cm of end systolic circumferential fiber length

Statistical analyses were performed using conventional methods for small samples [24]

Results

The results of the study appear in Table I and Figs 1 to 5 The group of 10 patients with MS consisted of five males and five females ranging from 27 to 53 years (mean 39 5) three with chronic atrial fibrillation and seven in sinus rhythm The calculated mitral valve area varied between 0 3 cm and 1 3 cm (mean 0 8) with the gradient across the mitral valve ranging from 9 to 28 mm Hg (mean 19) The mean pulmonary pressures varied from a near normal mean of 25 mm Hg to a high of 55 mm Hg (mean for the group 38)

To provide a group of similar RV load there were six patients with atrial septal defect three males and three females aged 12 to 40 years (mean 34 2) with a mean shunt across the septal defect of 4 22 L/min and mean pulmonary artery pressures ranging from 17 to 53 mm Hg (mean 42 7) Of the 10 normal subjects five were male and five female aged 15 to 58 years (mean 27 3) The mean pulmonary pressure ranged from 9 to 27 (mean for the group 18)

The five males and two females in the cardio

normal. There were no differences between the five patients with MS taking digitalis and the five who were not. The Frank-Levinson index, for example, was 1.28 ± 0.07 in the former and 1.25 ± 0.06 in the latter. Similarly small and statistically insignificant differences between these subgroups were found for all other variables being studied.

The state of the left ventricular myocardium was further explored in terms of its relaxation properties. As noted in Fig. 5, all of the indices of isovolumic relaxation indicate a defect in myocardial relaxation properties in cardiomyopathy but none in mitral stenosis or atrial septal defect.

Discussion

The idea of a myocardial factor in rheumatic heart disease is an old one. Indeed, prior to the development of cardiac valve surgery, it was stated by a number of authorities that symptomatology in rheumatic heart disease was due to myocardial involvement and that the valve lesions were quite incidental.[25, 26] After the advent of commissurotomy, it was obvious that the symptoms in the case of mitral stenosis were due to the valve lesion itself. However, some patients with a diagnosis of mitral stenosis suffered symptoms disproportionate to the demonstrable valve narrowing or did not experience the expected improvement with surgery.

Harvey and colleagues compared eight patients who benefited from surgery with an equal number who did not and concluded that the former, all characterized by pulmonary hypertension preoperatively, suffered chiefly from mitral valve obstruction, while the latter, characterized preoperatively by a low and fixed cardiac output, represented a syndrome in which the myocardial involvement was chiefly responsible for the symptomatology. The authors predicated an involvement based on persistent myocarditis. Although this study has been widely quoted, it must be noted that it was based on a small sample of patients, that no left heart data were available, that it has not been confirmed, and that the hypothesis of a persistent myocarditis was purely speculative.

The general acceptance thereafter of the idea that the left ventricle in mitral stenosis was normal is indicated by the number of investigative groups which used the mitral stenotic left ventricle experimentally as an example of the functionally normal left ventricle.[31, 38] However, the notion of a myocardial factor persisted, partly because of disparities between the expectations and results of cardiac surgery[37, 4] and partly because of various demonstrations of "left ventricular dysfunction" in mitral stenosis. With very few exceptions, the dysfunction reported was nothing more or less than the long recognized deficit in performance of the left ventricle in mitral stenosis as a volume pump. As stated above, low stroke volume has been recognized to be characteristic of mitral stenosis since the earliest investigations into the hemodynamics of this lesion. The more recent reports have simply involved new ways of describing a reduced ejection. Thus, the left ventricle in mitral stenosis has been shown to exhibit a subnormal contraction on cinefluorography,[8, 1] depressed left ventricular function curves based on rest and exercise stroke volumes in relation to filling pressures, low ejection fraction,[6, 8, 9, 11, 42, 43] subnormal response to isometric exercise,[8] and a diminished mean Vcf. As emphasized above, these measures represent new ways of describing a performance deficit which most workers have attributed entirely to the constraints imposed by the stenotic valve and the overloaded right ventricle. The low output, in any case, cannot be taken as evidence of a contractile deficit in the left ventricular myocardium since the left ventricle can pump no more blood than it is permitted to receive as a result of the performance of the overloaded right ventricle and in the presence of a stenosed inlet valve.

The only demonstration of a deficit in left ventricular function based on velocity-force considerations is that of Krayenbuehl and coworkers, who found a depressed Vmax obtained by linear retrograde extrapolation of Vce calculated as (dP/dt)/28P. However, no significant difference between normal subjects and patients with mitral stenosis was found by Frank and Levinson[6] using their volume normalized estimate of Vce. Moreover, in none of the various studies of performance cited above has there been any evidence in mitral stenosis of dilatation of the left ventricle or of elevation in resting end-diastolic pressure. Although Kasalicky and Feigenbaum[2] and their colleagues reported an abnormal rise in left ventricular filling pressure in some mitral stenosis patients during exercise, consistent with possible diminution in compliance, most investigators have found normal

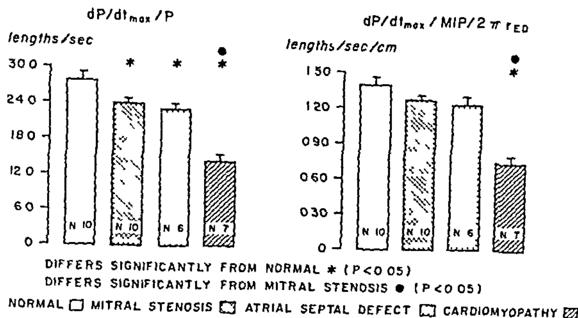


Fig 4 Indices of left ventricular contractility in various groups

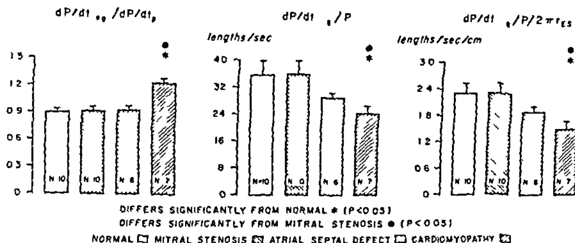


Fig 5 Various indices of LV isovolumic relaxation in normals and three patient groups

myopathy group ranged in age from 30 to 47 years (mean 37 7) and had mean pulmonary artery pressures ranging from 10 to 21 mm Hg (mean for the group 14 9)

As seen in Figs 1 and 2, there was no significant difference with respect to heart rate end diastolic pressure mean aortic pressure LV preload (end diastolic volume) and afterload (mean systolic tension) among the four groups

All three patient groups exhibited depressed LV pump performance as shown (Fig 3) by the data for stroke volume and ejection fraction This figure shows also that the three patient groups did not differ among themselves with respect to the depressed pump function

However differences were observed in measures of contractile element function (Fig 4) As expected, the mean value for Vce at dP/dt max in cardiomyopathy, 14 muscle lengths/sec was significantly below the normal mean of 28 muscle lengths/sec In mitral stenosis where the state of the myocardium is at issue a slightly but significantly depressed mean value of 24 muscle lengths/sec was observed Indeed in some reports it is from data such as these that a myocardial lesion in MS has been claimed However a subnormal contractile element velocity 23 muscle lengths/sec insignificantly different from that in mitral stenosis was also seen in ASD a disease in which no myocardial lesion has been demonstrated or hypothesized Moreover when the estimated contractile element velocity is normalized for initial fiber length or preload as in the Frank-Levinson index shown in the right panel normal contractility is seen in ASD as expected subnormal contractility is seen in cardiomyopathy as expected and the value in MS is seen to be the same as in ASD and in the

relaxation MS was indistinguishable from ASD a lesion in which no inflammatory or traumatic LV pathology is posited We conclude that reduced LV ejection in MS is not due to diffuse LV myocardial damage since the LV myocardium in that disease functions normally during the isovolumic phase of both contraction and relaxation

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filling pressures during both active leg exercise[4,6] and isometric hand exercise[8]

Thus it would appear that physiologic evidence for a myocardial factor is based on performance data, which bear no necessary relation to pathology in the left ventricular myocardium, and upon Vmax measurements, the validity of which is a matter of controversy. Evidence against the concept is the demonstration that left ventricular myocardial perfusion, oxidative metabolism, isovolumic relaxation, preload and contractility, measured as Vce at peak dP/dt and by the index of Frank and Levinson, are all normal in mitral stenosis. However, there is one report of possible importance in explaining the low cardiac output in this disease. Heller and Carleton[43] described in 20 of 25 patients angiographic evidence of a rigid mitral complex immobilizing the posterobasal area of the left ventricle. This anatomic phenomenon had previously been reported by Kirch[46] who found a significant shortening of the posterior wall of the left ventricle in most hearts from mitral stenosis patients studied at autopsy. Grant[47] confirmed this finding and suggested that leaflet thickening and chordal fibrosis produce a rigid cylinder of scar tissue which results in immobilization and consequent atrophy of the posterior wall. Heller and Carleton,[43] although they believe this rigid valve complex impairs contraction and underlies reduced stroke volume, point out that the lesion is unique to mitral stenosis and that its 'focal character speaks against diffuse lesions such as old rheumatic myocarditis.'[43] Moreover, without pressure tension or stress measurements, it is clear, as Scheuer[45] has pointed out, that angiography cannot measure contractility.

With regard to the surgical evidence for a myocardial factor, it will be recalled that Harvey and colleagues[1] first predicated the idea of a persistent myocarditis on the basis of comparison between mitral stenosis patients who improved with commissurotomy and others who did not. However, Selzer and Cohn[4] have pointed out that the long latency between the initial rheumatic fever attack and cardiac symptomatology makes persistent rheumatic activity an improbable explanation for any myocardial factor, and that speculation about a myocardial factor on the basis of poor surgical results is a fundamentally incorrect premise because such results cannot distinguish mechanical from myocardial factors.[29] Certainly the failure of patients to improve after mitral valvulotomy or replacement may well be attributable to other valve lesions which were undiagnosed or the severity of which was inadequately appreciated preoperatively,[48,49] to the fact that neither valve replacement nor valvuloplasty is capable of restoring fully normal valve function, or to intraoperative or postoperative surgical problems.[50,51]

Thus, in the critical test case of mitral stenosis, it is clear that a preoperative deficit in left ventricular performance exists but may be due entirely to the stenosis itself, to right ventricular overload, to increased pulmonary vascular resistance, to chronic atrial fibrillation, and possibly to the rigid 'mitral complex' described by Heller and Carleton.[43] No myocardial factor need be invoked and none has been conclusively demonstrated.

Summary

Subnormal stroke volume (SV) and ejection fraction (EF) in mitral stenosis (MS) have been attributed to abnormality in the left ventricular (LV) myocardium despite studies in this laboratory showing normal LV myocardial contractility and oxidative metabolism. To clarify this problem, LV function was studied in 10 patients with pure MS, seven with cardiomyopathy (MYO) who had normal LV preload (end diastolic volume) and afterload (mean systolic tension), six with atrial septal defect (ASD), and in 10 normal subjects (N). All three patient groups were characterized by subnormal SV, EF and contractile element velocity (Vce) at peak dP/dt despite normal preload and afterload. However, the Frank-Levinson contractility index, which normalizes Vce for diastolic fiber length, was depressed only in MYO (0.73 ± 0.07 vs 1.39 ± 0.07 in the N, $P < 0.001$), the values in MS (1.26 ± 0.04) and ASD (1.22 ± 0.07) differing insignificantly from N and from each other. Moreover, the ratio of peak negative to positive dP/dt, a recently proposed index of LV relaxation, although abnormal in MYO (1.23 ± 0.03), differed insignificantly among N (0.89 ± 0.04), MS (0.91 ± 0.05) and ASD (0.95 ± 0.04), as did several other measures of relaxation (e.g., velocity of fiber lengthening with and without normalization for end systolic fiber length). Thus, in LV pump performance, contractility and isovolumic

relaxation MS was indistinguishable from ASD a lesion in which no inflammatory or traumatic LV pathology is posited We conclude that reduced LV ejection in MS is not due to diffuse LV myocardial damage since the LV myocardium in that disease functions normally during the isovolumic phase of both contraction and relaxation

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The value and limitations of echocardiography in recording mitral valve vegetations

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The valvular vegetation is the basic pathologic lesion of infective endocarditis [1,2] Recent reports have stressed the usefulness of the echocardiogram in the noninvasive detection of such vegetations [3-11] In spite of the frequent occurrence of endocarditis however the total number of case reports of echocardiographically demonstrable proven vegetations is few and the sensitivity and specificity of echocardiography in their detection is uncertain

Within a recent eight month period we have seen three patients in whom severe cardiac decompensation developed in the setting of nonenterococcal streptococcal endocarditis All had pathologically documented vegetations of the mitral valve However what were considered technically satisfactory echocardiographic examinations showed evidence for a vegetation in only two of the three patients The case reports of these three patients serve to illustrate both the usefulness and the limitations of echocardiography in the detection of valvular vegetations

Methods

Echocardiographic examinations were per formed using a Smith Klıne Instruments Ekoline 20A echograph interfaced with a Honeywell 1856 Fiber Optic Visicorder and having a frequency output of 2 25 MHz per second and a repetition rate of 1000 pulses/second A 7 5 or 10 cm focused transducer was placed in the standard transducer position along the left sternal border and appropriately angled for examination of the left ventricle mitral valve and aortic root [3] The calibration was 1 cm in vertical distance and 0 1 second in horizontal duration

Case reports

Case 1 A B (202 31 78) was a 58 year old man with a history of an innocent systolic murmur He was without cardiac symptoms until July 31 1975 when he was admitted to the hospital because of fever and low back pain of two weeks duration Streptococcus viridans endocarditis was documented and intravenous penicillin therapy begun After two weeks worsening biventricular heart failure with a murmur of mitral regurgitation developed despite adequate antibiotic ther apy

An echocardiogram revealed a normal appearing mitral valve except for a definite dense echo recorded between the anterior and posterior leaflets which suggested an abnormal mass near the mitral orifice most likely a vegetation (Fig 1)

The congestive heart failure remained refractory to intensive therapy Cardiac catheterization and angiography confirmed severe mitral regurgitation with no valve calcification or systolic prolapse and a systolic ejection fraction of 48 per cent After a total of four weeks of antibiotic therapy the patient underwent mitral valve replacement

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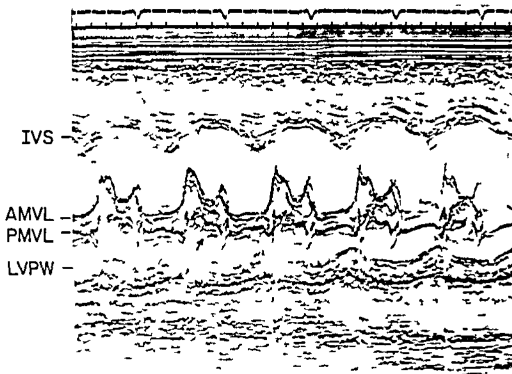


Fig 1 *Case 1* Echocardiogram of the left ventricle at the level of the mitral leaflets showing distinct dense echo (*arrow*) posterior to the anterior mitral valve leaflet Dense echo is most evident in diastole and is lost when the leaflets approximate in systole *IVS* = interventricular septum *AMVL* = anterior mitral valve leaflet *PMVL* = posterior mitral valve leaflet *LVPW* = left ventricular posterior wall



Fig 2 *Case 1* Surgically excised glistening mitral valve with the dark vegetation attached Anterior mitral valve leaflet is at the bottom and left Posterior mitral valve leaflet is at the top and right

The mitral valve appeared myxomatous with glistening and translucent leaflets and no fibrosis or calcification The leaflets were not redundant and the chordae tendineae were not elongated A partially calcified vegetation 2 cm in diameter with an irregularly pitted surface was present on the atrial surface of the anterior leaflet (Fig 2) Several smaller vegetations of similar character were scattered over both mitral leaflets and the chordae tendineae Two small chordae were ruptured at the site of vegetations

On microscopic examination the large vegetation showed diffuse areas of calcification Fibrin necrotic debris and numerous clusters of gram positive cocci were present within the vegetation without evidence of organization The smaller vegetations showed similar microscopic features Scattered areas of metachromatic staining and loss of normal architecture of the connective tissue suggestive of myxomatous degeneration [13] were present in portions of the valve leaflets and chordae uninvolved by vegetations

Immediately after the operation the patient s cardiac status was excellent but he succumbed two weeks later because of renal and respiratory complications

Case 2 R M (066 29 60) was a 68 year old woman with long standing mitral stenosis and atrial fibrillation The patient had mild congestive heart failure and had been satisfactorily maintained on digoxin and sodium warfarin She was admitted to the hospital on June 10 1975 with a history of three days of increasing dyspnea She was found to be febrile and in severe biventricular failure with a murmur of mitral stenosis

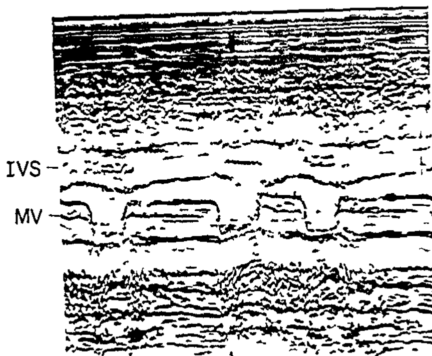


Fig 3 *Case 2* Echocardiogram showing the flat E F slope and reduced diastolic excursion of the mitral valve suggesting significant mitral stenosis No distinct echo posterior to the anterior leaflet is recorded *IVS* = inter ventricular septum *MV* = mitral valve

unchanged from prior examinations All blood cultures grew *Streptococcus bovis* and penicillin therapy was initiated Despite intensive therapy her condition worsened

An echocardiogram indicated significant mitral stenosis with a flattened E F slope less than 5 mm/sec and parallel diastolic motion of the anterior and posterior mitral leaflets with a reduced total diastolic excursion (Fig 3) Multiple echoes recorded from the mitral valve were considered to be consistent with valve thickening and calcification No unusual echoes suggesting a vegetation or a left atrial mass were recorded with repeated scanning from the mitral valve to the aortic root utilizing routine variation in the gain settings

The patient continued in a low output state and died on the fifth hospital day At necropsy both mitral leaflets were thickened and focally calcific with shortened thickened chordae tendineae On the atrial surface of the anterior leaflet extending from the closure line was a soft 1 5 cm in diameter lobulated vegetation (Fig 4) which occluded almost the entire mitral orifice Microscopic examination confirmed the presence of calcification of the mitral leaflets in addition to fibrous thickening and vascularization compat

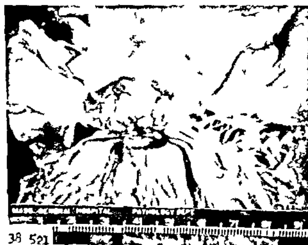


Fig 4 *Case 2* Postmortem specimen of the heart opened along the lateral wall Vegetation is seen seated on the anterior mitral valve leaflet Posterior leaflet is to the right The left atrium is above and the left ventricle is below Rheumatic changes in the valve apparatus can be seen to the right of the vegetation

ible with healed rheumatic valvulitis [4] The occluding vegetation was composed of necrotic debris blood elements and numerous colonies of gram positive cocci without organization No calcium was deposited within the vegetation

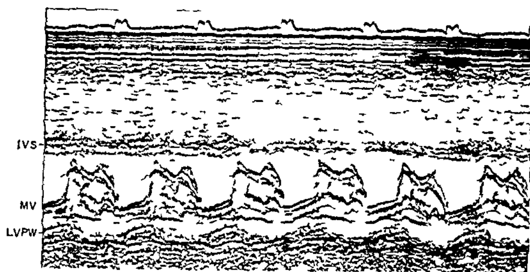


Fig 5 *Case 3* Echocardiogram at the level of the mitral valve leaflets Multiple dense echoes are recorded from anterior and posterior valve leaflets and distinct echoes are seen between the leaflets in diastole (*arrow*) *IVS* = interventricular septum *MV* = mitral valve *LVPW* = left ventricular posterior wall



Fig 6 *Case 3* Continuous echocardiographic scan from mitral valve to the aortic root Dense echo is seen within the left atrium in systole (*arrow*) at the level of the aortic leaflets and was thought to represent a prolapsing vegetation on the mitral valve *IVS* = interventricular septum *MV* = mitral valve *AV* = aortic valve *LA* = left atrium

Case 3 G S (205 02 00) was a 63 year old man admitted to the hospital on January 7 1976 with a three month history of fever and progressive weakness following a dental extraction performed without antibiotic coverage He was found to have *Streptococcus viridans* endocarditis After two weeks of adequate penicillin therapy his fever persisted Increasing biventricular heart failure developed and a prominent mitral regurgitation murmur was noted

An echocardiogram showed normal excursion of the mitral valve leaflets but multiple dense echoes, some moving with and some distinctly between the leaflets were recorded (Fig 5) During systole, a dense echo continuous with the anterior mitral valve leaflet could be detected within the left atrium even at the level of the aortic valve leaflets (Fig 6) The abnormal multiple echoes were thought to represent one or more vegetations on partially flail mitral valve leaflets

Left ventricular cineangiography demonstrated severe mitral regurgitation with a systolic ejection fraction of 40 per cent The mitral leaflets appeared focally thickened with a suggestion of systolic prolapse No valvular calcification was seen Because of refractory heart failure the patient underwent mitral valve replacement after a total of four weeks of antibiotic therapy

At operation the mitral leaflets were found to be flail because of ruptured chordae tendineae The excised leaflets were shiny and translucent Along the free edge of the anterior leaflet was an irregular gritty vegetation 0 7 by 0 5 by 0 3 cm in

size (Fig 7) Several smaller vegetations were scattered on the chordae tendineae some at the site of chordal ruptures

On histological examination the vegetations consisted of a central core of necrotic debris inflammatory cells and many colonies of gram positive cocci Scattered foci of calcification were evident within the vegetation Minimal organiza tion and healing were present along the basal and lateral borders of the vegetation No abnormali ties including calcification fibrous thickening or myxomatous degeneration were noted in the leaflets or chordae uninvolved by the infectious lesions

The patient died two months after surgery because of renal failure and recurrent infection

Discussion

The mortality rate in patients with bacterial endocarditis complicated by valvular dysfunction and congestive heart failure is high [1] [ ] [1] Deteri oration is most often a consequence of valvular incompetence due to the erosive effect of the organism Unusually large vegetations may result in additional complications such as orifice obstruction or leaflet distortion [1] [6] For this reason it would be desirable to noninvasively localize the site of endocarditic lesions allowing early institution of appropriate medical and/or surgical management

Dillon and co workers first noted that vegeta tions may present echocardiographically as shag gy echoes attached to a heart valve or as nonuni form thickening of the heart valves They suggested that such abnormal echoes were distinct and should not be confused with either valvular thickening from chronic rheumatic endocarditis or multiple echoes from a left atrial myxoma A review of the known case reports of echocardiographically demonstrable valvular vegetations having pathologic confirmation shows 29 on aortic valves [3] one on a tricuspid valve and ten on mitral valves [1] The first and third patients in this report confirm the usefulness of the echocardiogram in visualiz ing vegetations on mitral valves although the echoes recorded may not be specific for a vegeta tion A flail leaflet without vegetations may produce echoes in the left atrium during systole similar to those shown in Fig 6 A case report of vegetations partially obstructing a previously

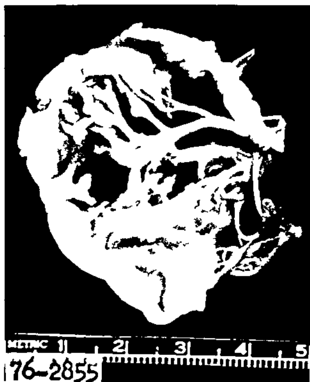


Fig 7 *Case 3* Surgically-excised mitral valve with multiple ruptured chordae tendineae Numerous vegetations are scat tered over the valve with the largest vegetation in the center of the free edge of the anterior leaflet Posterior mitral valve leaflet is above

stenotic mitral valve by Spangler and co workers is similar to our second patient These authors proposed that high gain settings may reveal abnormal echoes which although not specific would in the proper clinical setting most likely represent a vegetation However others have demonstrated similar echoes by increasing the gain of the instrument in patients with mitral stenosis alone and a left atrial myxoma may also mimic a vegetation echocardiographically [18] Therefore we feel such echoes can be artifacts of the high gain settings and do not necessarily suggest the presence of a vegetation

Vegetations as small as 0 2 cm have been detected by echocardiography [3] but size alone does not insure a successful recording The acoustic impedance of a mass relative to that of adjacent structures is of critical importance in its echocardiographic visualization [3] In our cases calcification of the vegetation as well as the nature of the mitral valve structure itself were more important determinants of echocardio

graphic detection than the size of the vegetation Echoes were recorded from calcified vegetations in Cases 1 and 3, which were distinct from the echoes of the noncalcified regurgitant mitral valves In Case 2, the echoes from the calcified stenotic mitral valve dominated and possibly masked, separate echoes from the large obstructing noncalcified vegetation The smaller calcified vegetations on flailing leaflets in Case 3 were seen, but the larger noncalcified vegetation on stenotic leaflets in Case 2 was missed

No prior echocardiographic case report has discussed the implications of calcification of a vegetation which is a basic part of the healing process in infectious endocarditis [20] Some of the previously reported patients with endocarditis had been fully treated and the vegetations seen were presumably healed and calcified We propose that calcification contributes to echocardiographic detection and in part explains the shaggy and fuzzy echoes described In addition, two serially studied patients have been reported to show an increase in the size and intensity of echoes from a vegetation with time despite bacteriologic cure [1] This was attributed to progressive valve thickening but may also have been a result of calcium deposition occurring with healing On the other hand technical factors alone can artifactually produce similar variations

Organization of a vegetation is a slow process, which may continue for months following clinical cure [0] In contrast, patients with active endocarditis and more severe clinical courses tend to have larger vegetations consisting primarily of acute inflammatory reaction [2] The histopathology of these vegetations may render them less suitable for echocardiographic detection, in spite of their size Our three patients did have active endocarditis and the vegetations found had not healed, however in two diffuse calcification had occurred Such early calcium deposition has been previously demonstrated in areas of bacterial necrosis without evident organization and is reported to be accelerated by antibiotic therapy but the pathogenesis of this early calcification is unexplained [0]

In conclusion the echocardiographic manifestations of mitral valve vegetations are varied and when present may be nonspecific This report illustrates that the inability to record distinct echoes suggestive of a vegetation does not necessarily exclude the presence of even a sizeable vegetation This is shown in an early stage of active endocarditis and when the site of involvement was a previously damaged, calcified and stenotic mitral valve Calcification of a vegetation can occur early and independently of the healing process, and may be an important determinant of echocardiographic visualization Additional studies of patients with endocarditis are needed to further assess the sensitivity and specificity of the echocardiogram for valvular vegetations and to clarify the role of calcification of vegetations in enhancing their echocardiographic detection

Summary

The echocardiographic findings and case reports of three patients with active Streptococcal endocarditis and severe congestive heart failure are presented All three had pathologically proven vegetations on the mitral valve however only the two with calcification of the vegetations were successfully demonstrated on echocardiography Clinical and pathological differences are highlighted and prior case reports in the literature are reviewed The nonspecific nature of echoes recorded from valvular vegetation is stressed and factors in their echocardiographic detection are discussed

We wish to thank Harriet J Walker for her assistance in the preparation of this manuscript

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Atrial septal defect of secundum type in the middle-aged

Clinical results of surgery and correlations between symptoms and hemodynamics

Kolbjorn Forfang M D
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Atrial septal defect of secundum type (ASD II) holds a unique position among the congenital cardiac malformations In spite of a steady improvement in diagnostic capabilities in recent years the diagnosis is sometimes not made until old age due to lack of symptoms and minor physical signs[1] It is generally accepted that children with uncomplicated ASD II and a significant left to right shunt should be operated on[2-4] The operative risk is small and the benefit is in most cases a normal life In middle aged or old patients however the justification for an operation in those individuals who are asymptomatic is questionable On the other hand, the benefit of surgery in a patient with major symptoms heart failure and atrial fibrillation may also be questionable Several reports[7-11] indicate clinical and hemodynamic improvements following operation However in most materials the number of middle aged patients is small and the method of material selection is not often obvious

Our study comprises nearly all Norwegians with ASD II operated on after 40 years of age Thus this material gives us the opportunity to study all the clinical aspects of ASD II in middle aged patients before and after surgery in an unbiased national sample of this disease

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Material and methods

Included in this study are 98 of the 100 patients who underwent surgery for ASD II above the age of 40 years in Norway up to January 15 1972 All patients except those not included were operated on in our hospital Seventy three of the patients were female and 25 were male with ages ranging from 40 to 64 years mean age 49 1 years The patients were studied preoperatively and early postoperatively and a prospective follow up study was started in July, 1972

The preoperative data are obtained from the medical records with additional information obtained at interviews during the follow up In 77 cases the preoperative hemodynamic examinations were made in our hospital and the results are reviewed by one of us (K F) In the remaining 21 cases the heart catheterizations were performed in other hospitals

Pressure recordings were obtained by right heart catheterization with zero reference level in the anterior axillary line in the fourth intercostal space In 89 cases the recordings included pulmonary capillary venous (PCV) pressure or left atrial (LA) (18 cases) pressure In 6 patients (4 before and 2 after surgery) all with normal pulmonary arterial (PA) pressure diastolic PA pressure was used as the PCV mean pressure Oximetry determinations were made in all cases The oxygen content was derived from the oxygen saturation and the oxygen capacity which was estimated from the hemoglobin concentration The shunt ratio $\dot{Q}_p/\dot{Q}$ was calculated from the formula

$$\frac{[O_2]\,Ao - [O\ ]\,SVC}{[O\ ]\,PV - [O\ ]\,PA}$$

$[O_2]$ = blood oxygen content Ao = aorta SVC = superior vena cava PA = pulmonary artery PV = pulmonary vein $[O\ ]\,PV$ calculated from oxygen saturation 95% where blood samples from PV were not obtained

Pulmonary arteriolar resistance (PAR) was calculated from the ordinary formula

$$\frac{PAMP - PCVMP \text{ (or LAMP) (mm Hg)}}{\dot{Q}_p \text{ (ml per second)}}\ 1332 \text{ (dyn sec cm } \text{)}$$

$PAMP$ = pulmonary artery mean pressure $PCVMP$ = pulmonary capillary venous mean pressure $LAMP$ = left atrial mean pressure $\dot{Q}_p$ = pulmonary flow obtained from Fick s formula

$$\frac{\text{Oxygen consumption}}{[O\ ]\,PV - [O_2]\,PA}$$

Three operative techniques have been used during the period (1) Suturation in conventional hypothermia (28 to 30° C) (2) direct suturation or suturation using a prosthetic patch in extracorporeal circulation and (3) closure by the circumclusion technique described by Sondergaard and colleagues [2] In the hypothermia cases the exclusion of circulation lasted from 2 to 8½ minutes and in all these cases oxygenated blood was infused into the coronary artery system and into the distal part of the aorta via another cannula distal to the arterial clamp

A follow up examination was made from 22 to 174 months (mean 74) after the operation in all of the 88 patients who were alive at that time It included an interview clinical examination electrocardiogram (ECG) phonocardiogram spirometry and an x ray of the heart In addition hemodynamic studies were performed in 82 cases (Right heart catheterization at rest and during exercise including hydrogen test for detecting small left to right shunts oximetry pressure recordings and cardiac output measurements by means of Fick s method) The ECG radiological and hemodynamic data will be published in detail elsewhere

The main symptoms were graded as follows

1 Arrhythmia symptoms—0 No symptoms of arrhythmia I Palpitations II Paroxysmal tachyarrhythmias III Feeling of permanent irregular rhythm We have used the subjective arrhythmia symptoms rather than the actual rhythm on the ECG recording because it was thought to be more relevant to the clinical application The electrocardiographical correlates to the symptoms were—0 Regular sinus rhythm I Periods of frequent supraventricular extrasystoles II Paroxysmal supraventricular tachycardias III Permanent atrial fibrillation

2 Dyspnea—0 No dyspnea I Dyspnea which only occurred during heavy exertion was however thought to be more marked than in healthy people at the same age II Dyspnea which slightly limited the physical activity III A marked limitation of physical activity but no dyspnea at rest IV An inability to carry on any physical activity without dyspnea and dyspnea which may even occur at rest

3 Edema + Intermittent or permanent pitting edema

4 Chest pain + A pain syndrome partly related to exercise consisting of a burning pressing or a sharp stinging sensation located retrosternally or on the left side of the chest mostly of longer duration than typical angina pectoris

5 Fatigue + An otherwise unexplained increa ed feeling of fatigue

Information about the patient deaths in the follow up period were obtained from the family doctors or from the local hospital where the patients died

The clinical diagnosis of cerebral embolism was made in cases characterized by acute onset of neurological signs of a cerebral lesion lasting for more than half an hour and observed by others than the patient

The statistical method used was the Student s *t* test

Results

Diagnosis of heart disease The age at which a diagnosis of heart disease was made ranged from 1 to 60 years mean 31 6 ± 14 3 (S D) In 27 patients the diagnosis was made by routine chest x ray examination (During that period all adult Norwegians had a compulsory routine chest x ray after a 2 to 10 years interval) In 45 patients other routine examinations led to the diagnosis while only 26 patients consulted a physician because of symptoms which might have been related to ASD

The age at onset of *the first symptom* is difficult to assess However the age the patients said—to the best of their recollection—that they

Atrial septal defect of secundum type in the middle-aged

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Table I Coexistent anomalies other heart and pulmonary diseases

Anomaly/heart pulmonary disea es	*Number of patients*
CS drainage to LA	1
LSVC drainage to LA	1
LSVC drainage to CS	2
Double IVC one drainage to CS	1
Anomalous PV drainage to SVC only	3
SVC and RA	4
RA only	10
Mitral stenosis (Lutembacher s syndrome)	1
Tricuspid regurgitation†	2
Aortic regurgitation	1
Mitral regurgitation	1
Myocardial infarction	1
Hypertensive heart disease	1
Sequelae after pulmonary tuberculosis	3
Pulmonary fibrosis	1
Pulmonary arteriovenous aneurysm	1
Chest deformity (rachitis)	1

Mitral ommissurotomy in connect on w th ASD-operat on
†I one patient Beall prosthetic valve was impl nted in connecti n w th ASD-operation
Abbrev ati ns CS = coronary sinus LA = left atrium LSVC = l ft superio en ca SVC = superior ena ca a IVC = inferio vena cava PV = pulm nary vein RA = right atrium

Table II Early complications of surgery (tachy arrhythmias not included) (23 patients)

Complications	*Number of patients*
Preoperative cerebral lesion	5
Upper RPV ligated preoperatively (extensive bleeding)	1
Right sided diaphragmal paralysis	1
Hematothorax (reoperated)	1
Large right to-left shunt	1
Pulmonary embolism	3
Cerebral embolism	1
Mesenterial embolism (Laparotomy 14 day)	1
Aortic embolism (bifurcature) (Embolectomy 3 day)	1
Gastrointestinal bleeding (anticoagulated low TT)	1
Postpericardiotomy syndrome	10
Sepsis/endocarditis†	4
Atrioventricular block (pacemaker temporari ly)	1

This pat ent had one month previously been operated on in con entional hypothermia but ASD closure was impossible without extracor pore l circulation
†After operation the inferior vena cava was drained to the left atrium and this was corrected on reoperation
Abbreviations RPV = right pulmonary vein TT = Thrombotest

Ten patients had paroxysmal atrial fibrillation exclusively in the early postoperative period In seven patients tachyarrhythmias were converted by synchronized DC shock

Hospital stay after surgery in the 95 patients who were discharged alive ranged from 10 to 141 days mean 29 Twenty nine patients stayed for more than 30 days

Late deaths Seven patients died during the follow up period (Table III) and three of them were unrelated to heart disease

The follow up study comprised all 88 patients who were alive at the beginning of the study Six patients refused heart catheterization In the remaining 82 patients a residual shunt was found in 13 The relation between residual shunts and surgical methods is shown in Table IV In all the number of patients with a residual shunt was 15 (17 2 per cent) of the 87 patients evaluated (including two late deaths and the three hospital deaths in which necropsy was done) The frequency of residual shunts was highest in patients operated by suturation in conventional hypothermia The next in frequency were patients who had closure of a large ASD by means of a prosthetic patch In one patient operated on with the circumclusion technique a single anomalous pulmonary vein draining to the superior vena cava was left uncorrected by the surgeon (residual shunt ratio 1 8)

Table III Late deaths

Sex	*Age at Death*	*Year of oper ation*	*Month after operation*	*Cause of death*
M	61	1959	111	Endocarditis heart failure
F	60	1965	86	Cerebral hemorrhage†
F	61	1969	30	Cerebral embolism‡
F	57	1970	13	Sudden unexpected death
F	50	1963	10	Breast cancer
M	52	1965	66	Acute leukemia
F	63	1969	25	Acute pancreatitis

Residu l shunt, ratio 1.2.
†Four years after ASD operat on reoperated with closure of residual shunt (atio 2.2) and implantation of Beall tricuspid valve prosthesis. Thrombotest was 5 per cent on ant coagulant therapy
‡Paroxysmal atrial fibrillation

Symptoms before and after surgery

Before assessing the symptoms we had excluded all patients with concomitant heart or pulmonary disease Before surgery 84 remained for evaluation At the follow up an additional 10

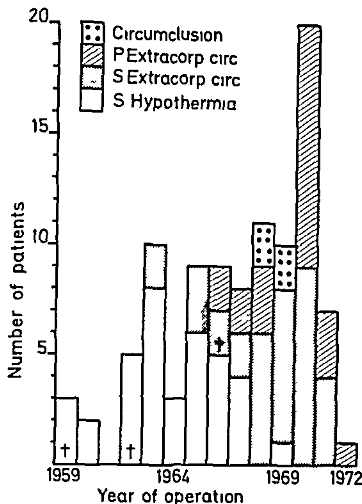


Fig 1 Number of patients operated on in each year with an indication of the surgical methods used and the number of hospital deaths S direct suturation P suturation using a prosthetic patch The crosses indicate hospital death

recognized their first significant symptom ranged from 5 to 59 years mean 33 Ten patients had no symptoms at all and seven of these were picked up by *the routine chest x ray examination*

The preoperative hemodynamic study revealed a shunt ratio ranging from 1 6 to 7 9 mean 3 21 ± 1 21 (S D) Thirty one of the 93 patients had a PA mean pressure above 20 mm Hg but only one had *obstructive pulmonary hypertension*, i e increased PAR above 250 dyn sec cm [5] (PA mean pressure 40 mm Hg *PAR 329)* The time period between the hemodynamic examination and operation ranged from 1 to 144 months Twenty six patients were operated within 3 weeks and only 5 patients had to wait for more than 1 year

Types of ASD According to the peroperative findings the defects were divided into 3 groups

1 Sinus venosus type (high secundum defect) in 24 patients

2 Central defect (' *foramen ovale defect*) in 66 patients and

3 Low secundum defect (inferior vena cava type extending down to the entrance of the inferior vena cava) was found in 8 patients

Coexisting anomalies other heart and pulmonary diseases are shown in Table I All patients with anomalous pulmonary vein drainage to the superior vena cava had a sinus venosus defect The six patients with pulmonary disease were reckoned to have pulmonary symptoms in addition *to the ASD symptoms*

Year of operation surgical methods used and hospital deaths are shown in Fig 1 Two patients were twice operated The first operation was performed in conventional hypothermia but closure of ASD was technically impossible without extracorporeal circulation They were reoperated after one and five months, respectively The second operation appears in Fig 1

Three patients died during their hospital stay after the operation, *i e* a hospital mortality rate of 3 per cent

1 A 43 year old man with myocardial infarction one year prior to the operation died suddenly 6 days after the operation Necropsy showed *acute myocardial infarction The preoperative PA* mean pressure was 15 mm Hg

2 A 46 year old woman died from hypotension and cardiac arrest on the second postoperative day The preoperative PA mean pressure was 14 mm Hg

3 A 55 year old man in whom the operation was started with ligation of a left superior vena cava draining to the left atrium When closure of the ASD was attempted, an AV block with severe bradycardia occurred *Sinus rhythm was re* established when the sutures were loosened but after the operation he was severely ill with a cerebral lesion pulmonary and renal failure and died on the tenth postoperative day PA pressure was *not* obtained preoperatively Systolic RV pressure however, was 65 mm Hg

All these patients were at work before the operation and all belonged to functional Class II according to the criteria of the New York Heart Association (NYHA) [5] There were no deaths among the last 65 patients who were operated on

Early complications of surgery are shown in Table II All three patients with arterial embolism had paroxysmal atrial fibrillation postoperatively Tachyarrhythmias without secondary complications are not included in this table One patient temporarily had a sick sinus syndrome

Table VI Dyspnea before and after surgery

Before surgery			After surgery: Grading of dyspnea in the follow up material (n = 55) (No of patients)				
Grading of dyspnea	*Total material (No of patients)*	*Follow up material (No of patients)*	*0*	*I*	*II*	*III*	*IV*
0	17	11	10	1	0	0	0
I	22	17	12	5	0	0	0
II	28	20	11	8	1	0	0
III	16	6	2	3	1	0	0
IV	1	1	0	1	0	0	0
Total	84	55	35	18	2	0	0

Grading of dyspnea See methods

Table VII Edema chest pain and fatigue before and after surgery

Before surgery				After surgery: Grading of symptoms in the follow up material (n = 55) (No of patients)	
Symptoms	*Grading*	*Total material (No of patients)*	*Follow up material (No of patients)*	–	+
Edema	–	69	49	48	1
	+	15	6	4	2
Total		84	55	52	3
Chest pain	–	0	44	44	0
	+	14	11	10	1
Total		84	55	54	1
Fatigue	–	70	44	44	0
	+	14	11	10	1
Total		84	55	54	1

patients without additional lesions now belong to class I or II and 32 of 55 (58 1 per cent) have no symptoms at all This table also includes the patients with residual shunt but their improvement is not so striking One patient who had a residual shunt (ratio 2 2) had deteriorated and had to be reoperated later on

Relation between preoperative symptoms and arrhythmias The relation between arrhythmias and dyspnea edema and functional class (NYHA) is shown in Table IX Individuals with permanent atrial fibrillation (III) showed an increased frequency of dyspnea of Grade II and III and edema in comparison with the other patients They therefore also belong to the higher functional classes Patients with paroxysmal tachyarrhythmias (II) had the same frequency of dyspnea and edema as patients who did not have arrhythmias (0) or palpitations (I) No significant correlation was found between arrhythmias and chest pain or feeling of fatigue

Acute cerebral lesions Prior to surgery two patients had had an acute cerebral lesion In one of them—who had had paroxysmal atrial fibrillation—the clinical course suggested a cerebral embolism As mentioned above one patient with paroxysmal atrial fibrillation had a cerebral embolism in the early postoperative period The acute cerebral lesions appearing in the follow up period seem to be related to the presence of arrhythmias Three of the 19 patients with permanent atrial fibrillation had cerebral embolism compared to 1 of the 76 patients without this arrhythmia

Prior to the operation none of the patients had received anticoagulant therapy At the follow up however the seven patients on this therapy were found to have atrial fibrillation (five permanent

Table IV Residual shunt related to surgical method

Surgical method	Number of patients: No residual shunt	Q_p/Q_s 1 2 2	$Q_p/Q_s > 2$	Total
Suturation hypothermia	23	6(1)	0(1)	29(2)
Circumclusion	2	1	0	3
Suturation extracorp circulation	27	2	1*	30
Patch extracorp circulation	17	3	0	20
Total	69	12(1)	1(1)	82(2)

Reoperated see text
In parenthesis are two of the late deaths in whom residual shunt was demonstrated by heart catheterization

Table V Arrhythmia symptoms before and after surgery

Before surgery: Grading of arrhythmia symptoms	Total material (No of patients)	Follow up material (No of patients)	After surgery: Grading of arrhythmia symptoms in the follow up material (n = 55) (No of patients): 0	I	II	III
0	28	22	19	1	1	1
I	19	13	8	4	0	1
II	26	18	7	1	8	2
III	11	2	0	0	0	2
Total	84	55	34	6	9	6

Grading of arrhythmia symptoms 0 No arrhythmia I Palpitations (extrasystoles) II Paroxysmal tachyarrhythmias III Permanent irregular rhythm (atrial fibrillation) See text

patients were excluded because of acquired lesions (mitral regurgitation, two patients arterial hypertension, either on antihypertensive therapy or diastolic blood pressure continuously above 105 mm Hg five patients coronary heart disease two patients and chronic bronchitis one patient) Furthermore we excluded the patients with a residual shunt and the patients who were not hemodynamically examined, in whom residual shunt can not be excluded as emphasized by others[14, 26] Thus the group in which pre and postoperative symptoms can be compared consisted of 55 patients The postoperative symptoms were evaluated after a complete postoperative recovery

Arrhythmias The distribution of the different types of arrhythmia symptoms appears in Table V Concerning the follow up material the distribution is shown both before and after surgery Before surgery 56 of 84 patients (66 7 per cent) had arrhythmias The number of patients suffering from palpitations or paroxysmal tachyarrhythmias after surgery is halved compared to the preoperative level but four additional patients had a permanent irregular rhythm (atrial fibrillation) When the early postoperative period was taken into account 78 of all 98 patients (79 6 per cent) (patients with concomitant heart or pulmonary disease included) had had arrhythmias at least once

Dyspnea Table VI shows the degree of dyspnea before and after surgery There was a considerable improvement of this symptom After surgery only 2 of the patients had dyspnea which slightly limited physical activity whereas the remaining 53 had little or no dyspnea

Edema The number of patients with peripheral edema was reduced after surgery as shown in Table VII

Chest pain was a striking symptom in several patients prior to surgery (Table VII) In all but one this symptom disappeared after surgery

Fatigue As demonstrated in Table VII the fatigue disappeared in all but one of the patients after surgery

Functional class (NYHA) *The functional classifications are presented in* Table VIII The improvement after surgery is striking All

Discussion

Our material gave an opportunity to examine nearly all patients in a well defined population both before and after closure of ASD II Consequently the material represents a consecutive unbiased sample of middle aged patients with ASD II Only nine individuals recommended for surgery in this age group were not operated on for various reasons and a follow up of these cases will be published

Many patients were aware of their heart disease from early childhood and some also had had symptoms for several years before surgery Until 1959 however surgery was not done in such patients in Norway The first symptoms relating to ASD occurred at different ages from 5 to 59 years Ten patients were asymptomatic This is in accordance with other reports [2] [1] and reflects the great variability in tolerance of the heart and the pulmonary vessels to the hemodynamic burden of atrial septal defect This must be kept in mind in the evaluation of the individual patient

The survey of surgical methods used (Fig 1) also shows changes in surgical techniques from 1959 to 1972 We found a residual shunt in 15 of the 87 patients (17 2 per cent) As might have been expected the frequency of residual shunt was highest in cases where conventional hypothermia was used because the time available to the surgeon was only a few minutes There was also a high frequency of residual shunt among patients with a large ASD necessitating a prosthetic patch In other reports [9] [15] [1] [26] a residual shunt was found in 5 to 34 per cent of the patients Persistent left to right *shunts are often* unsuspected [2] and consequently a hemodynamic examination is necessary to evaluate the real number of cases

In other reports[3] [14] [2] [21] [3] *the figures of* hospital mortality rate in patients above 40 years of age varies between 0 and 26 per cent but most of them are similar to the 3 per cent in our series The three patients who died were not older and did not have a higher PA pressure than the average There were no deaths among the last 65 patients, and this appears to be a reflection of the improvement in operative technique and postoperative care

The frequency of concomitant heart and pulmonary diseases was high in our material Only a pure ASD material can be used when evaluating the late effects of closure of ASD and therefore several patients have been excluded in this study

Arrhythmia symptoms were frequent before surgery and showed lesser degrees of regression after surgery than the other symptoms The number of patients complaining of palpitations or paroxysmal tachycardia was halved None of the patients with permanent atrial fibrillation prior to surgery developed sinus rhythm afterwards and an additional four patients had atrial fibrillation In the early postoperative period supraventricular tachycardias were frequently seen and had to be terminated by DC shock in seven patients Our findings are in accordance with several reports [2] [16] [7] [32] [3] which indicate increasing frequency of arrhythmias with age This is very important because of the connection between the arrhythmias and the serious arterial emboli which are frequent in these patients In our material there were six acute cerebral lesions thought to be emboli of whom five occurred after surgery Five of these occurred in patients with atrial fibrillation either permanent or paroxysmal There is however little knowledge available concerning the incidence of arrhythmias many years after surgery during childhood We believe however that at least some of the cerebral emboli might have been avoided by surgery at an earlier stage It seems reasonable to recommend anticoagulant therapy in all *patients with ASD II* complicated with arrhythmias whether they are operated on or not

In patients with atrial fibrillation we have found significantly higher RA and LA (PCV) mean pressures compared to other patients That may be a consequence of right ventricular failure but also of left ventricular failure which is often found in middle aged patients with ASD II as emphasized by several authors [4] [16] The high filling pressure may lead to atrial fibrillation disappearance of atrial contractions and thereby a further increment of the mean atrial pressure in *order to sustain* the high ventricular end diastolic pressure required In these patients the findings of an increased frequency of edema and high degrees of dyspnea and functional class (Table IX) might have been expected

We found the symptoms before surgery to be unrelated to the size of the left to right *shunt* Dyspnea was related to pressure increments both in RA RV PA and LA (PCV) (Table X) and this reflects the differences in hemodynamic consequences of a *left* to right shunt Similar

Table VIII Functional class (NYHA) before and after surgery

Funct class	Before surgery: Total material (No of patients)	Before surgery: Follow up material (No of patients)	After surgery: Funct class in the follow up material (n = 55) (No of patients) I	II	III	IV
I	11	9(1)	9(1)	0	0	0
II	54	39(6)	21(1)	18(5)	0	0
III	18	6(3)	2	4(2)	0	0(1)*
IV	1	1	0	1	0	0
Total	84	55(10)	32(2)	23(7)	0	0(1)

In parenthesis are those patients with residual shunt on follow up
*Residual shunt ratio 2 2 reoperated

Table IX Relationships between arrhythmia symptoms and dyspnea, edema and Functional Class (NYHA) before surgery

Symptoms and grading of symptoms	Grading of arrhythmia symptoms (No of patients) 0	I	II	III	Total
Dyspnea					
0	9	2	6	0	17
I	9	4	7	2	22
II	6	9	9	4	28
III	4	3	4	5	16
IV	0	1	0	0	1
Total	28	19	26	11	84
Edema					
–	26	15	23	5	69
+	2	4	3	6	15
Total	28	19	26	11	84
Functional class					
I	9	1	1	0	11
II	15	14	20	5	54
III	4	3	5	6	18
IV	0	1	0	0	1
Total	28	19	26	11	84

Grading of symptoms See method

two paroxysmal) and none of them had had any acute cerebral lesion

Pulmonary hypertension (PA mean pressure above 20 mm Hg) was found in four patients after surgery compared to 31 of 93 patients before operation The only patient with elevated PAR before surgery improved from functional Class IV to II, and pulmonary arterial mean pressure fell from 40 to 32 mm Hg The PAR however increased from 329 to 697 dyn sec cm

Relation between symptoms and age and hemodynamic data before surgery are shown in Table X No significant correlations between the shunt ratio and the different degrees of the symptoms were found It appears that increasing degrees of the symptoms arrhythmias dyspnea edema and functional class (NYHA) are significantly correlated to increasing RA, RV, PA, and PCV pressures and to increasing PAR Patients with permanent atrial fibrillation and high functional classes (III and IV) were significantly older than the others

Relation between symptoms and age and postoperative hemodynamics At follow up all patients belonged to functional Class I (32 patients) or Class II (23 patients) and there was no significant hemodynamic differences between these groups either at rest or during exercise The mean age at operation was significantly higher in Class II patients compared to Class I (50 7 years ± 1 6 (S E M) and 46.8 ± 1 0 respectively $p < 0\ 05$)

The relation between working capacity and functional class (NYHA) before and after surgery is shown in Table XI where all living patients are included i e disregarding other heart/pulmonary diseases and residual shunts There was a poor correlation between functional class and working capacity Sixteen patients who were at work before the operation had a disability pension during the follow up period Five of these had other heart or pulmonary diseases and four had cerebral lesions (three of these occurred during the operation) In one a grave psychoneurosis lead to disability one had a disability pension despite a functional improvement (functional Class III to II) and three men had disability pensions in spite of being able to work and having only minor symptoms both before and after surgery

Discussion

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In other reports[3, 5, 16, 1, 22] the figures of hospital mortality rate in patients above 40 years of age varies between 0 and 26 per cent[3] but most of them are similar to the 3 per cent in our series The three patients who died were not older and did not have a higher PA pressure than the average There were no deaths among the last 65 patients and this appears to be a reflection of the improvement in operative technique and postoperative care

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II	54	39(6)	21(1)	18(5)	0	0
III	18	6(3)	2	4(2)	0	0(1)*
IV	1	1	0	1	0	0
Total	84	55(10)	32(2)	23(7)	0	0(1)

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Table X Hemodynamic data and age at different degrees of the symptoms

Types and grading of symptoms	RAMP (mm Hg) n	RAMP ± SEM		RVSP (mm Hg) n	RVSP ± SEM		PAMP (mm Hg) n	PAMP ± SEM		PCVMP/LAMP (mm Hg) n	PCVMP/LAMP ± SEM		Shunt ratio Q_p/Q_s n	Shunt ratio ± SEM	
Arrhythmia symptoms															
0-I	46	2.1 ± 0.38		46	33.4 ± 2.04		46	16.7 ± 1.29		46	4.7 ± 0.49		47	3.17 ± 0.15	
II	26	2.0 ± 0.42	a, a	26	36.7 ± 3.31	a	25	18.1 ± 1.44	NS	25	5.9 ± 0.81	a	26	3.23 ± 0.[illegible]7	NS
III	11	5.7 ± 1.44		11	43.1 ± 4.05		10	21.7 ± 2.98		11	9.1 ± 1.90		11	3.33 ± 0.3[illegible]	
Dyspnea															
0	17	1.7 ± 0.57		17	32.9 ± 2.94		16	13.8 ± 1.42		16	4.9 ± 1.29		17	3.38 ± 0.20	
I	22	1.9 ± 0.58	a, a	22	28.6 ± 2.15	a, c, a	22	14.6 ± 1.56	b, c	22	4.6 ± 0.63		22	3.06 ± 0.3[illegible]	NS
II	27	2.6 ± 0.52		27	37.6 ± 3.30		27	19.0 ± 1.60		28	5.6 ± 0.72	a	28	3.42 ± 0.20	
III	16	4.4 ± 1.03		16	43.1 ± 3.40		15	22.9 ± 2.05		15	8.3 ± 1.27		16	2.92 ± 0.24	
IV	1	1.0		1	72.0		1	40.0		1	3.0		1	1.9	
Edema															
−	69	1.9 ± 0.27	a	69	32.7 ± 1.54		67	16.1 ± 0.89	b	68	4.9 ± 0.43		69	3.25 ± 0.13	NS
+	14	5.5 ± 1.24		14	50.7 ± 4.37		14	25.4 ± 2.54		14	9.2 ± 1.53		15	3.01 ± 0.31	
Chest pain															
−	70	2.5 ± 0.38	NS	70	35.9 ± 1.84	NS	67	17.7 ± 1.07	NS	68	5.5 ± 0.53	NS	70	3.20 ± 0.13	NS
+	13	3.0 ± 0.69		13	34.9 ± 3.73		14	17.9 ± 1.90		14	6.6 ± 0.92		14	3.24 ± 0.33	
Funct Class (NYHA)															
I	11	2.3 ± 0.66		11	30.3 ± 2.79		11	13.4 ± 1.73		11	4.8 ± 1.69		11	3.38 ± 0.22	
II	53	2.1 ± 0.37	a	53	33.6 ± 2.00	a, b	52	16.5 ± 1.07	b, c	53	4.9 ± 0.41	b	54	3.26 ± 0.16	NS
III	18	4.2 ± 0.93		18	43.4 ± 3.44		17	22.9 ± 2.01		17	8.9 ± 1.31		18	3.00 ± 0.26	
IV	1	1.0		1	72.0		1	40.0		1	3.0		1	1.9	

a = 0.05 > p > 0.01 b = 0.01 > p > 0.001 c = p < 0.001 NS = p > 0.05
Abbreviations RAMP = right atrial mean pressure RVSP = right ventricular systolic pressure PAMP = pulmonary artery mean pressure PCVMP = pulmonary capillary venous mean pressure LAMP = left atrial mean pressure PAR = pulmonary arteriolar resistance
Grading of symptoms See method

Table XI Relationships between working capacity and Functional Class (NYHA) before and after surgery

Functional class (NYHA)	Number of patients: Heavy work	Medium heavy work	Light work	Temporary disabled	Disability pension	Total
Before surgery						
I	2	5	3	0	1	11
II	7	34	19	2	1	63
III	1	8	10	3	1	23
IV	0	0	0	0	1	1
Total	10	47	32	5	4	98
After surgery						
I	7	25	7	0	5	44
II	1	20	6	0	11	38
III	0	0	0	0	5	5
IV	0	0	1	0	0	1
Total	8	45	14	0	21	88

Residual shunt and/or other significant heart or pulmonary disease in addition to ASD

findings have been made by Gault and co workers[11] and by Dave and co workers.[14]

Chest pain localized retrosternally which was partly related to exercise angina pectoris type was a striking symptom in 14 of the 84 patients (16.7 per cent) in our series. The pain was completely relieved by surgery in all but one patient. These figures are similar to those found

	PAR dyn sec cm			Age (years)		
	n	± SEM		n	± SEM	
	46	74 7 ± 9 0	NS	47	47 6 ± 1 0	
	25	77 [illegible] ± 9 8		26	48 6 ± 1 3	
	10	88 7 ± 9 9		11	5[illegible] 5 ± 1 8	
	16	48 7 ± 5 7	b	17	47 1 ± 1 3	NS
	2[illegible]	64 4 ± 6.3		22	46 6 ± 1.3	
	[illegible]	80 0 ± 9 [illegible]		[illegible]8	49 2 ± 1 [illegible]	
	15	104 5 ± 15 7		16	50 [illegible] ± 1 9	
	1	3[illegible]9 0		1	64 0	
	67	68 9 ± 5 4		69	48 0 ± 0 8	NS
	14	116 6 ± 20 7		15	51 3 ± 1 8	
	6[illegible]	8 9 ± 6.7	NS	[illegible]0	48 2 ± 0 8	NS
	14	68 8 ± 14 3		15	51 3 ± 1 8	
	11	41 [illegible] ± 5 9	c	11	45 3 ± 1 5	
	5[illegible]	[illegible]1 ± 5 8		54	48 4 ± 0 8	
	17	101 2 ± 14 0		18	50 [illegible] ± 1 7	
	1	3[illegible]9 0		1	64 0	

in other materials where this symptom is mentioned[3, 11, 3] We believe that this pain syndrome in some way is caused by the ASD and not by concomitant coronary artery disease No specific hemodynamic correlate to this symptom was found

As judged by functional class before and after surgery there was a remarkable improvement after surgery in most of the patients who had significant symptoms Even in asymptomatic patients there was a subjective improvement following correction presumably because these patients thought their preoperative condition was normal The improvement was *independent of* preoperative pulmonary hypertension but only one of our patients had obstructive pulmonary hypertension Reports from other centers[7, 2] indicate a very high operative mortality rate in patients with severe pulmonary hypertension but in moderate pulmonary hypertension the figures are similar to ours

The main goal for any therapy should be to give the patient a better quality of life and preferably to sustain his working capability We have not found any good correlation between functional class and work capacity either before or after surgery This is mostly thought to be due to different psychosocial factors working independently of the effects of the ASD Psychological hindrances which often follow open heart surgery as indicated by Heller and co workers[31] may be of importance in this respect The number of patients with disability pension at follow up is mainly caused by cerebral lesions as a complication to ASD and other diseases The three nearly asymptomatic men with disability pension represent a special psychosocial problem in our country with a modern social security legislation

Individuals with ASD II should preferably be operated on during childhood as the operative risk is small and the benefit is an almost normal life Middle aged patients disabled by ASD II can expect a marked improvement after surgery In asymptomatic middle aged patients it is probably not so hazardous to postpone surgical treatment until significant symptoms arise That delay may however increase the risk of arrhythmias and thereby cerebral embolism

Summary

This study comprised 98 of 100 patients above *40 years of age* who underwent surgery in Norway for atrial septal defect of secundum type (ASD II) up to 1972 A follow up study was performed on average 74 months (range 22 to 174) after surgery *Pulmonary* hypertension was found in 30 per cent The pulmonary arteriolar *resistance* (PAR) was increased in only one patient *Increasing* degrees of arrhythmias dyspnea edema and functional class (NYHA) before surgery were significantly correlated to increasing *pressures in* the right atrium right ventricle pulmonary artery (PA) left atrium (pulmonary capillary venous pressure) and to increasing PAR No significant correlations between the shunt ratio *and different* degrees of the symptoms were found The hospital mortality rate was 3 per cent *and was not related* to high age or increased PA *pressure* There were no deaths among the last 65 *patients*

Before surgery 13 per cent of the patients were in functional Class I and 22 6 per cent in Class III *or IV* The corresponding figures after surgery were 58 1 per cent and 0 per cent The frequency of arrhythmias was high and this was the symptom which showed the least improvement Cerebral embolism occurred in six patients who also had arrhythmias and five of the embolisms occurred after surgery

All patients with ASD II complicated with arrhythmias should be given anticoagulant therapy, whether they are operated on or not In middle aged patients disabled by ASD II, a marked improvement after surgery can be expected

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Influence of test site on ventricular fibrillation threshold

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Determination of ventricular fibrillation threshold (VFT) is a frequently used method of assessing vulnerability to arrhythmias in experimental animals The original method was developed by Wiggers and Wegria and involved repeated scans of the cardiac cycle with 10 msec duration pulses of increasing amplitude They demonstrated that VFT lowered in animals with occlusion of the coronary arteries and because of this concluded that the measurement was a reflection of vulnerability to arrhythmias Later Han and Moe found that a wide variety of agents which increased disparity of ventricular recovery properties a condition expected to enhance reentrant activity also decreased VFT The exact relationship of measured values of VFT to naturally occurring arrhythmias is however incompletely understood The measurement is influenced not only by underlying electrophysiologic properties of the ventricle but also by the method used to determine it In more recent studies trains of stimuli rather than single pulses have been used for VFT determination These methods have the advantage that they decrease the time required for repeated scans of the cardiac cycle Tamargo and associates however have recently demonstrated interactions of the sequential stimuli delivered during the relative refractory period which could cause VFT measured with trains to be either higher or lower than VFT measured with single pulses

VFT is also influenced by the test site used to make the determination Shumway and associates [7] using a single pulse method and Yoon and associates [8] using gated trains for determining VFT found that under control conditions VFT measured at right ventricular sites is lower than VFT measured at left ventricular sites Shumway and associates also found that following coronary occlusion a decrease in VFT could be demonstrated if single test pulses were applied to an ischemic area but not if they were applied to sites distant to ischemic areas Han using gated trains of stimuli was unable to demonstrate a difference in VFT whether measured at sites within an ischemic area or at sites 10 to 12 mm away from the border of an ischemic area

This report presents further evidence obtained both from studies on experimental animals and from a computer simulation of ventricular fibrillation threshold that in the presence of localized areas of shortened ventricular recovery properties VFT is dependent on the test site used to make the measurement A possible mechanism for the dependence of VFT on test site location is also suggested

Methods

Experimental animals Experiments were performed on 19 mongrel dogs anesthetized with pentobarbital 30 mg per kilogram The dogs were ventilated with a fixed volume respirator the chests opened with a sternal splitting incision and the hearts suspended in pericardial cradles A multichannel digital stimulator with constant current or constant voltage output stages which was designed and constructed in our laboratory was used to deliver basic driving stimuli and test

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stimuli for measuring VFT and refractory periods The sinus node was crushed, and the right atrium paced at fixed cycle lengths of 330 to 500 msec VFT was measured with gated trains of stimuli delivered to bipolar electrodes with inter electrode distances of 2 to 3 mm The trains of stimuli had frequencies of 100 Hz 5 msec duration pulses and were delivered after every ninth atrial driving stimulus The trains were set to start immediately after the QRS complex and to end just after the peak of the T wave and had durations of 170 to 230 msec During the course of each experiment the timing of the trains was kept constant with respect to atrial driving stimuli The intensity of trains of stimuli was increased in 0 5 mAmp increments until fibrillation was induced VFT measurements were made at sites at the margin of localized lesions at sites distant to the lesions, and in some instances at sites within the lesions Measurements during control periods were alternated with those made in the presence of the lesions and measurements were repeated at at least one of the test sites to determine if the preparation was stable After fibrillation was induced defibrillation was accomplished within 15 seconds by applying a 10 watt second countershock through paddles applied directly to the heart In six dogs the lesion was an ischemic area produced by temporarily occluding one or more branches of the anterior descending coronary artery In these experiments VFT measurements were started 2 minutes after coronary occlusion, and were completed within 3 minutes The coronary occlusion was then released Previous studies from our laboratory have demonstrated that even after repeated occlusions VFT returns to control values following release of occlusions of this duration [9] Spontaneous arrhythmias were rarely observed, if they occurred the animal was excluded from the study In the remaining 13 animals the 'lesion' was an area of altered recovery properties induced by circulating water at 0°, 10° 15° 25°, 45° or 50° C through a chamber 2 5 cm in diameter which was sutured to the anterior surface of the left ventricle

In nine of the 13 experiments in which thermal lesions were employed in addition to VFT determinations, functional refractory periods and activation times were measured at sites adjacent to each of the VFT test sites These measurements were made during control periods and in the presence of the lesions Refractory period measurements were made by delivering basic driving stimuli to each test site and delivering two times diastolic threshold unipolar cathodal test stimuli to the same site after every other basic driving stimulus The test stimuli were initially delivered early in the cardiac cycle at a time when a response was not induced, and then delayed in 1 msec increments until a propagated response occurred The interval between the basic driving stimulus and the earliest test stimulus, delivered to the same site, that produced a propagated response represented the refractory period Times of activation of each of the VFT test sites were also measured during drive of each VFT test site Activation times were determined by recording electrograms from closely spaced, approximately 1 mm bipolar electrodes These electrodes were constructed of two strands of insulated silver wire that were spun in a helix and the insulation of two adjacent turns was stripped The electrodes were sutured to the epicardial surface of the ventricles adjacent to each VFT test site The activation time measurements and refractory period measurements were used to estimate differences in time of recovery between VFT test sites associated with drive of each VFT test site in both control states and in the presence of the localized areas of altered recovery properties

Computer simulation A computer model of ventricular fibrillation threshold based on a model reported by Moe Rheinboldt and Abildskov [10] was developed

The model consisted of a 40 by 40 matrix of simulated tissue units Recovery properties were randomly assigned with a range of values from 10 to 20 time units corresponding to known inhomogeneities of cardiac tissue, or individual units were assigned recovery properties with shorter average durations and an increased range of values 5 to 20 time units to simulate changes in refractory period associated with early acute coronary artery occlusion Recovery properties were modified by the preceding cycle length to simulate the effect of heart rate on refractory period Conduction velocity was not independently assigned to the model but propagation was delayed when excitation encountered relatively refractory units In the model fibrillation threshold was defined as the minimum duration

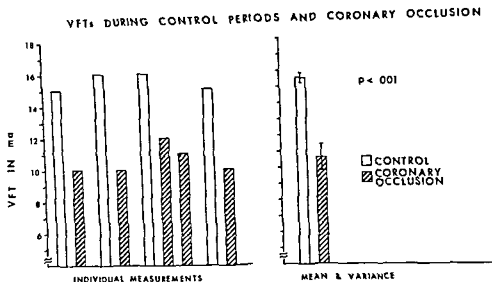


Fig 1 Bar graph showing VFT of one dog measured repeatedly during control periods and periods of coronary occlusion The test site was on the anterior surface of the left ventricle in an area that became cyanotic during coronary occlusion

of constantly available stimuli that induced self sustained temporally and spatially irregular activity Fibrillation threshold was measured at 49 test sites each consisting of a cluster of six tissue units evenly distributed throughout the matrix The simulated ischemic lesion comprised one sixteenth of the total matrix and was centrally located

Results

Coronary occlusion Values of repeated VFT s determined on one dog during control periods and during periods of coronary occlusion of from 2 to 5 minutes duration are shown in Fig 1 The measurements were made at a site on the anterior surface of the left ventricle that became cyanotic during coronary occlusion and control and occlu sion determinations were alternated Control VFT s averaged 15 5 ± 0 3 mA and during coronary occlusion VFT s averaged 10 7 ± 0 8 mA a statistically significant decrease at the $p < 0\,001$ level

Results of studies of the influence of test site location on the determination of VFT during coronary occlusion are illustrated in Fig 2 The data in this illustration were obtained during occlusions of eight coronary arteries in six dogs VFT was measured during control periods and during repeated temporary occlusions of the coronary arteries Test sites were in areas that became cyanotic during coronary occlusion at the margin of the cyanotic area and in a distant nonischemic area on the free wall of the right ventricle Average values of VFT measured at these sites during coronary occlusion are shown in the figure and are expressed as a per cent of control values VFT s determined at sites within the cyanotic areas fell by an average of 41 ± 4 2 per cent of control values a statistically signifi cant decrease in VFT at the $p < 0\,01$ level VFT determined at the margins of cyanotic areas fell by an average of 30 ± 18 6 per cent of control values $p < 0\,21$ When VFT was measured at sites distant to areas made cyanotic by coronary occlusion it was an average of 7 ± 29 per cent lower than control values an insignificant change These findings indicate that the well documented increase in arrhythmias associated with acute coronary occlusion is not reflected in VFT determinations when these measurements are made at test sites distant to an ischemic area and confirm the earlier report of Shumway and associates [2]

Computer simulation The influence of test site on VFT determination was also investigated with a computer simulation as discussed *in the* Methods section In the control state VFT mea sured at 49 test sites averaged *45 ± 15 time units* In the presence of the simulated ischemic lesion VFT measured at all test sites within the area of short recovery properties decreased to 20 time units However VFT s measured at sites outside

stimuli for measuring VFT and refractory periods The sinus node was crushed, and the right atrium paced at fixed cycle lengths of 330 to 500 msec VFT was measured with gated trains of stimuli delivered to bipolar electrodes with inter electrode distances of 2 to 3 mm The trains of stimuli had frequencies of 100 Hz, 5 msec duration pulses and were delivered after every ninth atrial driving stimulus The trains were set to start immediately after the QRS complex and to end just after the peak of the T wave and had durations of 170 to 230 msec During the course of each experiment the timing of the trains was kept constant with respect to atrial driving stimuli The intensity of trains of stimuli was increased in 0 5 mAmp increments until fibrillation was induced VFT measurements were made at sites at the margin of localized lesions, at sites distant to the lesions and in some instances at sites within the lesions Measurements during control periods were alternated with those made in the presence of the lesions and measurements were repeated at at least one of the test sites to determine if the preparation was stable After fibrillation was induced, defibrillation was accomplished within 15 seconds by applying a 10 watt second countershock through paddles applied directly to the heart In six dogs the lesion was an ischemic area produced by temporarily occluding one or more branches of the anterior descending coronary artery In these experiments VFT measurements were started 2 minutes after coronary occlusion, and were completed within 3 minutes The coronary occlusion was then released Previous studies from our laboratory have demonstrated that even after repeated occlusions VFT returns to control values following release of occlusions of this duration [9] Spontaneous arrhythmias were rarely observed, if they occurred the animal was excluded from the study In the remaining 13 animals the lesion was an area of altered recovery properties induced by circulating water at 0°, 10° 15° 25°, 45°, or 50° C through a chamber 2 5 cm in diameter which was sutured to the anterior surface of the left ventricle

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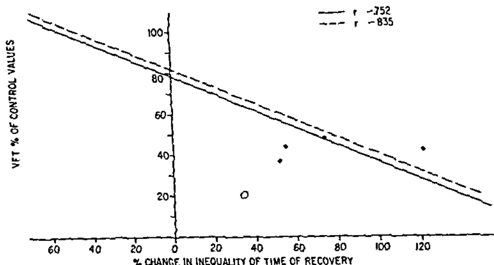


Fig 3 Graph showing the relationship of per cent change in inequality of time of recovery measured at sites close to VFT test sites that resulted from thermal lesions, to VFT expressed as a per cent of control values Each data point represents per cent change in inequality of recovery time associated with drive of a given VFT test site during experimental interventions in comparison to control values of inequality in time of recovery and VFT measured at that site during the intervention expressed as a per cent of control VFT In three instances with a given drive site there was less inequality in time of recovery in the presence of a lesion than in the control state In two of these instances VFT measured at these sites increased slightly and in the other instance it decreased by only 4 per cent Regression lines and correlation coefficients are shown These were calculated with and without the one circled data point

In some experiments in the presence of a lesion there was less inequality of time of recovery during drive of VFT sites distant to the warmed areas than there was with drive of the same site during control periods When this occurred VFT measured at these sites was not significantly changed from control measurements The data from these experiments are summarized in Fig 3 In this figure VFT's measured during alteration of recovery properties are expressed as a per cent of control values and are plotted on the vertical axis Inequalities of time of recovery during alteration of recovery properties are expressed as a per cent change from the inequalities in time of recovery during control periods and are plotted on the horizontal axis The graph shows that with alteration of recovery properties the greatest decrease in VFT occurred when measured at sites that when used to drive were associated with the greatest increase in inequality of time of recovery In three instances with drive of sites distant to a warmed area inequality in times of recovery decreased in the presence of the lesion VFT increased slightly over control values in two of these cases and in the other instance there was only a 4 per cent decrease in VFT in comparison to the control

Regression lines have been calculated including and excluding the one circled point on the graph The correlation coefficient of the relationship of inequality of time of recovery to ventricular fibrillation threshold was −0 835 if the one circled point was excluded from the calculation and was −0 752 if the circled point was included in the calculation

Discussion

An influence of test site on measured values of VFT is not unique to the setting of coronary occlusion Even under control conditions VFT is lower when measured at right ventricular sites than at left ventricular sites [6] and is lower when measured at sites on the posterior wall of the left ventricle than at anterior left ventricular sites [7]

The results of this study demonstrate that in the presence of localized areas of short recovery properties VFT measurements are highly dependent on the test site used in the determination This dependence of VFT values on test site was observed in animals with coronary occlusion in animals with areas of short recovery properties produced by warm thermal lesions and in a computer simulation of fibrillation threshold In the animal studies reported here the test stimuli

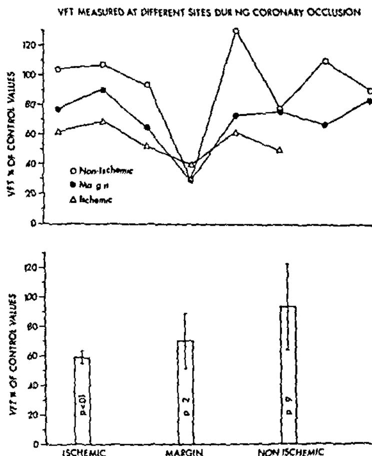


Fig 2 VFTs measured during occlusion of eight coronary arteries in six dogs are shown In the upper panel individual measurements expressed as per cents of control values are shown Measurements were made within at the margin of and at a site distant to the area that became cyanotic during occlusion In the graph in the lower panel the data have been averaged

of the area of simulated ischemia were unchanged from control VFT determinations These results from the computer simulation confirmed the results found in *experimental animals* with coronary occlusion

Effect of test site on dispersion in time of recovery and VFT A possible mechanism for these findings was that differences in activation and recovery sequences following application of test stimuli to various locations were associated with different degrees of inequality in time of recovery The sequence with the greatest inequality of time of recovery would be expected to have the lowest VFT For example following application of test stimuli to a site within an area of short recovery properties more dispersion in time of recovery would be expected than following application of test stimuli to a site distant to an area with short recovery properties

Experiments using thermal lesions to alter recovery properties were carried out to test this hypothesis In these experiments thermal lesions were used to alter recovery properties *Stable* conditions could be maintained for longer periods *of time using this method of altering* recovery properties than was possible with coronary occlusion In some experiments only VFTs were measured to determine if the differences in VFTs at various test sites, observed in dogs with coronary occlusion and the computer simulation, were also present with a thermal lesion model VFT's were measured alternately *during* control *periods* and during thermally induced changes in recovery *properties VFT test stimuli were* delivered to a site adjacent to the area of altered recovery properties or to a site on the free wall of the right ventricle distant to the area of altered recovery properties Warm thermal lesions which shorten refractory periods were used in five dogs VFT measured at sites near the warmed area decreased in comparison to control values in all animals with an average decrease of 69 ± 18 per cent *There was no significant change in comparison to* control values when VFT was measured at sites *distant to the warmed area In the presence of* cold lesions VFT decreased when measured either at sites near or distant to the lesion The decrease in VFT averaged 49 ± 22 per cent when measured at sites near the cooled area and averaged 52 ± 16 per cent when measured at distant sites a statistically insignificant difference in measurements at the two sites In nine additional experiments inequality in time of recovery associated with drive of the VFT test sites was estimated during control periods and following alteration of *recovery properties* with thermal lesions To do this during regular drive of each *VFT test site time of activation was determined from electrograms recorded from closely spaced bipolar electrodes at sites close to the VFT test* sites Refractory periods at these sites were also *determined* These determinations were made during control periods and during alteration of recovery properties and the inequality in time of recovery during drive of each site was estimated from these measurements For example if activation time at one site (A_1) occurred *60* msec after a basic driving stimulus (S_1) and refractory period at that site (RP_1) was *200* msec and activation at another site (A_2) was *10* msec after S_1 and its refractory period (RP_2) was 225 msec the inequality in time of recovery between the two sites would be estimated to be 25 msec

Inequality in time of recovery $= |(A_2 + RP_2) - (A_1 + RP_1)|$

Differences in the temporal relationship of time of recovery following application of VFT test stimuli to various locations are probably responsible for the observed differences in effects of lesions on VFT measured at these sites

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for measuring VFT were gated trains of stimuli It is possible that VFT measured in ischemic areas or in areas with warm thermal lesions decreased because refractory periods shortened and the trains of stimuli induced two responses rather than one response This possibility would not however, explain why VFT, measured with gated trains of stimuli delivered to sites distant to ischemic areas failed to decrease and reflect the known increase in vulnerability to arrhythmias associated with coronary occlusion Other investi gators, including Wiggers Wegria and Pinera and Shumway and associates[7] using a single pulse method have also demonstrated a decrease in VFT when the measurement was made at ischemic sites In addition Shumway and asso ciates[7] found that VFT s measured at sites distant to an ischemic area were not significantly different from control measurements Those investigators did not study the effect of stimulus site on VFT under other experimental conditions, and did not postulate a reason for their findings

In the present study, an influence of test stimulus site on measured values of VFT was demonstrated in animals with localized alteration of recovery properties induced by warm thermal lesions and with a computer simulation of fibril lation threshold as well as in experimental animals with acute coronary occlusion The most likely explanation for these findings is that differ ences in the temporal relationships of recovery times associated with delivery of test stimuli to various sites were associated with varying degrees of vulnerability to fibrillation Activation and recovery sequences associated with the least inequality of time of recovery would be expected to have higher VFT s than activation and recovery sequences associated with marked inequality of time of ventricular recovery In the presence of an area of short recovery properties less inequality in time of recovery would be expected if activation were initiated at a distance from that area than if activation were initiated within the area The experiments in which inequality in time of recovery associated with drive of a site was estimated before and after alteration of recovery properties and related to change in VFT measured at that site, support this possibility

In the experimental animals, when warm thermal lesions, which shorten refractory periods were used VFT decreased when measured near the lesion but not when measured at a distant site This finding was comparable to the finding in animals with temporary coronary occlusion which also shortens refractory periods and in the computer simulation in which refractory period shortening was simulated In the presence of cold thermal lesions, which prolong refractory periods VFT decreased in comparison to control values at all test sites used to make the measurements The reason for the lack of influence of test site location on VFT threshold in the presence of cold thermal lesions is uncertain Comparable changes in refractory period were present with both lesions Refractory period shortened by an average of 36 msec with the warm lesions and refractory period prolonged by an average of 42 msec with the cold lesions Cold slows conduction velocity as well as prolonging refractory periods and the conduction abnormalities within the cold spot may have been great enough that it was the major determinant of vulnerability to fibrillation Further studies of the relative influence of conduction velocity and inequality of recovery times on VFT would be desirable However it is difficult to find interventions applicable to exper imental animals that slow conduction velocity without also changing refractory periods At the present time conduction velocity is not an inde pendent variable in our computer simulation so investigation of this interesting question is delayed

The findings indicate that measurements of VFT are influenced not only by the intrinsic electrophysiologic properties in the ventricle but also by the temporal relationship of these proper ties to each other, and that application of VFT test pulses to various sites can influence these temporal relationships The results have implica tions in the design and interpretation of experi mental studies of VFT

Summary

An influence of VFT test site location on measured values of VFT was demonstrated in dogs with coronary occlusions in dogs with local ized areas of short recovery properties induced by warm thermal lesions and with a computer simu lation of fibrillation threshold Under these exper imental conditions VFT did not significantly change from control values when the measure ment was made at a site distant to the lesion

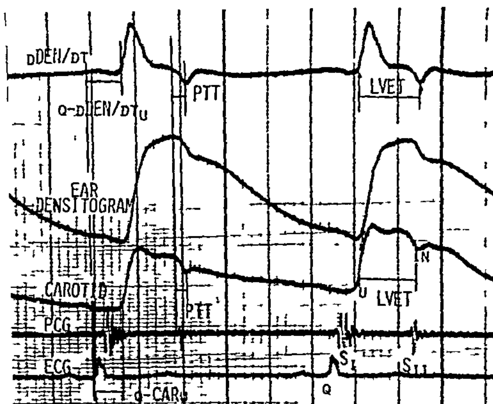


Fig 1 Densitographic and carotid-derived systolic time intervals Top to bottom densitogram derivative (dDEN/dt) ear densitogram curve carotid phonocardiogram (PCG) electrocardiogram (ECG) Q–dDEN/dt = time from "zero time" (Q) to derivative upstroke Q–CAR = time to carotid upstroke PTT = pulse transmission time. LVET = left ventricular ejection time U = upstroke In = incisura

with arm extended subjects were asked to squeeze the cuff as hard as possible Subjects were allowed three trials with the highest value achieved used as the subject s maximum voluntary contraction (MVC) Control recordings were taken after a 15 minute rest period in the chair The subjects then squeezed the cuff at 30 per cent MVC with recordings made prior to release at four minutes of IHG The same procedure was followed for 50 per cent MVC except that recordings were taken at the end but prior to release of one minute of IHG

Bicycle ergometry Bicycle ergometry at 50 100 and 150 watts was done on a separate morning The protocol for each load was identical twenty minute rest periods followed by control recordings preceded each bout of exercise Bicycle ergometry recordings were taken at four minutes of exercise—without interrupting the exercise for the recordings Recovery recordings with subjects seated on the bicycle ergometer were taken at 30 seconds one and five minutes

Recordings All tracings were recorded on a 8 channel Hewlett Packard recorder No 568 100A and included a simultaneous electrocardiogram (ECG) phonocardiogram (PCG) carotid pulse curve ear densitogram and first derivative of the ear densitogram A bipolar ECG was recorded via disposable electrodes pasted on the manubrium and lower sternum just above the xiphoid (attached to the right and left arm leads respectively) with a ground electrode (attached to the right leg lead) pasted on the subject s left midaxillary line below the costal margin The PCG was recorded at a nominal filter frequency of 50 Hz at the mesoapex via a Hewlett Packard model A/B contact microphone which was secured by an expansible strap The carotid pulse curve was recorded via a Hewlett Packard model A/B contact microphone and signal splitter All carotid tracings were recorded from the right carotid artery with the microphone held by an investigator A Hewlett Packard No 780 16 photoelectric ear piece with modified circuitry and power supply was used to record the ear densitogram The earpiece was secured over the

Systolic time intervals utilizing ear densitography

Advantages and reliability for stress testing

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The great advantages of electrocardiographic stress testing have justified its continued popularity Its limitations in diagnosis[1-3] and its greater limitations for assessing cardiac function have made it desirable to develop additional reliable noninvasive methods Post exercise determinations of systolic time intervals (STI) have provided valuable but limited data[4,5] Polygraphic recordings for STI during actual exercise performance reflect valuable functional responses,[6] but are limited to unusually cooperative subjects owing to movement and breathing artifact in the external displacement pulse curves Technical investigations of the ear densitogram and its first time derivative (dDEN/dt) have documented its validity for measuring the left ventricular ejection time[7]

LVET and the pre ejection period (PEP) are the fundamental STI Added together they represent electromechanical systole or EMS taken respectively as denominator and numerator they form the convenient ratio, PEP/LVET The purpose of this study was to evaluate in a new series the densitographic systolic time intervals during a wide variety of stresses Thus we report not only LVET for which we already had limited evidence[7] but also the equally important PEP Since the other intervals (q S_I and q S_{II}, or 'electromechanical systole) are measured from the accompanying phonocardiogram if PEP as well as LVET are reliably measured using the densitogram derivative, all STI can be determined without the carotid tracing At least two major advantages are apparent (1) reliable pulse tracings during all kinds of body movement, and (2) elimination of one 'pair of hands owing to the self retaining feature of the densitograph[8]

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Methods

Ten healthy males ages 22 to 35 years who had not previously been studied in our laboratory, volunteered with informed consent for this study All subjects had a normal electrocardiogram chest x ray, medical history, and physical examination

Subjects were studied on two separate mornings in the postabsorptive state one morning included the posture series and isometric hand grip exercise the other, bicycle ergometry

Posture series The recordings for the posture series commenced after a 15 minute rest period and included the following positions (1) supine recordings taken after the initial 15 minute rest period in supine position stated above (2) sitting recording taken two minutes after transition from supine to sitting position (3) standing recording taken two minutes after transition from sitting to standing position, (4) squat recording taken at onset of squat (from standing position) and again after two minutes of uninterrupted squatting

Isometric handgrip The IHG series followed the completion of the posture series above A rolled pressure cuff attached to a sphygmomanometer which contained a baseline pressure of 20 mm Hg was used for the IHG Seated in a chair

squatting positions showed LVETs had a correlation coefficient of +0 98 (p < 0 001) a slope of 0 99 msec/msec and an intercept at −5 47 msec

Control values for IHG for the two methods of measurement of LVET (subjects seated in a chair) showed a correlation coefficient of +0 97 (p < 0 001) a slope of 0 97 msec/msec and an intercept at 2 89 msec

IHG at 30 per cent and 50 per cent MVC (with subjects seated in a chair) yielded LVETs with a correlation coefficient of +0 97 (p < 0 001) a slope of 0 93 msec/msec and an intercept at 15 32 msec

Control values for bicycle ergometry (subjects seated on the bicycle ergometer) showed the LVETs had a correlation coefficient of +0 96 (p < 0 001) a slope of 0 96 msec/msec and an intercept at 6 88 msec

Bicycle ergometry during 50 100 and 150 watts yielded LVET with a correlation coefficient of +0 98 (p < 0 001) a slope of 0 93 msec/msec and an intercept at 12 31 msec

Recovery from bicycle ergometry at the three workloads above with measurements made at 30 seconds one and five minutes (with subjects seated on the bicycle) showed a correlation coefficient for the two LVETs of +0 98 (p < 0 001) a slope of 0 98 msec/msec and an intercept at 3 5 msec

When all data from the six conditions above were pooled the over all correlation coefficient was +0 98 with a slope of 0 98 msec/msec and an intercept at −0 22 msec

PEP (Fig 3) Since the PEPs were calculated from the same beats as those from which the LVETs were calculated the conditions and times at which the data for PEP are derived are identical to those stated above Analysis of carotid derived PEPs versus dDEN/dt derived PEPs showed the following results

Posture Series r = +0 98 (p < 0 001)
slope = 1 02 msec/msec
intercept = 4 02 msec
Control for IHG r = +0 91 (p < 0 001)
slope = 1 02 msec/msec
intercept = 3 44 msec
IHG r = +0 82 (p < 0 001)
slope = 0 ~2 msec/msec
intercept = 38 36 msec

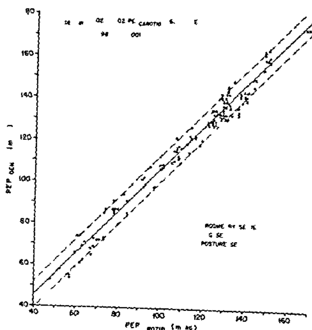


Fig 3 Correlation of pre-ejection period (PEP) from carotid curve (PEP) with PEP from densitogram derivative curve (PEP) r = +0 98 p < 0 001

Controls for
bicycle ergometry
r = +0 93 (p < 0 001)
slope = 1 09 msec/msec
intercept = −2 51 msec
Bicycle ergometry
r = +0 89 (p < 0 001)
slope = 1 01 msec/msec
intercept = 5 73 msec
Recovery from
bicycle ergometry
r = +0 97 (p < 0 001)
slope = 1 01 msec/msec
intercept = 5 73 msec
Over all analysis of
all data above
r = +0 98 (p < 0 001)
slope = 1 02 msec/msec
intercept = 4 02 msec

Discussion

The comparisons of carotid derived LVETs versus dDEN/dt derived LVETs and carotid derived PEPs versus dDEN/dt derived PEPs all showed highly statistically significant correlation coefficients (p < 0 001 for all comparisons made) with slopes displaying the very close tracking

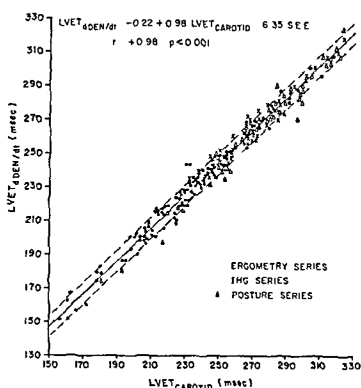


Fig 2 Correlation of left ventricular ejection time from carotid curve ($LVET_{CAROTID}$) with LVET densitogram derivative curve ($LVET_{dDEN/dt}$) r = +0 98 p < 0 001

pinna of the left ear with a gauze pad placed between the light source and the ear to prevent heat discomfort to the subjects The curve from the ear densitogram was differentiated to produce the first derivative of the ear densitogram (dDEN/dt) Since it has been demonstrated that dDEN/dt provides measurements of LVET which are closer to those of the conventional carotid measurements than are those of the undifferentiated ear densitogram curve [7] dDEN/dt was used for the measurements in this study (Fig 1)

Measurements The q wave of the ECG was the zero point for all time measurements The time from q to the mitral component of the first heart sound (Im) the second heart sound (II_A) the carotid upstroke (CARu), the carotid incisura (CAR_{IN}), the dDEN/dt upstroke ($dDEN/dt_u$)—measured at the point of rapid change in upstroke velocity,[7] and the dDEN/dt nadir ($dDEN/dt_n$)

Blinding procedure To avoid observer bias the measurements on the carotid pulse curves were measured blindly from those on the dDEN/dt curves

Calculations The carotid derived LVET was calculated as the time from the upstroke to the incisura of the carotid ($LVET_{CAROTID}$ = $CAR_{IN} - CAR_u$) and the dDEN/dt derived LVET was calculated as the time from the upstroke to the nadir of dDEN/dt ($LVET_{dDEN/dt} = dDEN/dt_n - dDEN/dt_u$)

The pulse transmission time (PTT) was measured for both the carotid and dDEN/dt curves as the time from II_A to the incisura and nadir respectively The pre ejection period (PEP) was then determined for those two curves by subtracting the corresponding PTT from the upstroke of that curve Thus, $PEP_{CAROTID} = CAR_u - PTT_{CAROTID}$ and $PEP_{dDEN/dt} = dDEN/dt_u - PTT_{dDEN/dt}$ *

Five beats were measured on each of the recordings of each subject The mean values of the five beats were the values used in the statistical analysis of the data

Statistical analysis *The statistical analyses of LVET for carotid versus dDEN/dt include the correlation coefficient (r), the slope (b), and the* intercept (a) of the relationship with carotid derived LVETs on the abscissa and dDEN/dt LVETs on the ordinate The analyses were separately determined for each of the following conditions (1) posture series including recordings in supine sitting standing and squatting positions, (2) controls for IHG with subjects seated in a chair, (3) IHG at four minutes for 30 per cent MVC and at one minute for 50 per cent MVC, (4) controls for bicycle ergometry with subjects seated on the bicycle, (5) bicycle ergometry at four minutes of exercise at 50 100, and 150 watts, and *(6) recovery from bicycle exercise at 30 seconds, one and five minutes with subjects seated on the bicycle An over all correlation* coefficient slope and intercept was also determined for all six conditions above combined

The statistical analysis for carotid derived PEP vs dDEN/dt derived PEP was the same as that for LVET

Results

LVET (Fig 2) Analysis of carotid derived *LVETs versus dDEN/dt derived LVETs showed* the following results

The posture series which included measurements of LVET in supine sitting standing and

* This method is mathematically identical to the more conventional calculation PEP = (q–S) –LVET but permits separate study of PTT

squatting positions showed LVETs had a correlation coefficient of +0.98 ($p < 0.001$) a slope of 0.99 msec/msec and an intercept at −5.47 msec

Control values for IHG for the two methods of measurement of LVET (subjects seated in a chair) showed a correlation coefficient of +0.97 ($p < 0.001$) a slope of 0.97 msec/msec and an intercept at 2.89 msec

IHG at 30 per cent and 50 per cent MVC (with subjects seated in a chair) yielded LVETs with a correlation coefficient of +0.97 ($p < 0.001$) a slope of 0.93 msec/msec and an intercept at 15.32 msec

Control values for bicycle ergometry (subjects seated on the bicycle ergometer) showed the LVETs had a correlation coefficient of +0.96 ($p < 0.001$) a slope of 0.96 msec/msec and an intercept at 6.88 msec

Bicycle ergometry during 50 100 and 150 watts yielded LVET with a correlation coefficient of +0.98 ($p < 0.001$) a slope of 0.93 msec/msec and an intercept at 12.31 msec

Recovery from bicycle ergometry at the three workloads above with measurements made at 30 seconds one and five minutes (with subjects seated on the bicycle) showed a correlation coefficient for the two LVETs of +0.98 ($p < 0.001$) a slope of 0.98 msec/msec and an intercept at 3.5 msec

When all data from the six conditions above were pooled the over all correlation coefficient was +0.98 with a slope of 0.98 msec/msec and an intercept at −0.22 msec

PEP (Fig 3) Since the PEPs were calculated from the same beats as those from which the LVETs were calculated the conditions and times at which the data for PEP are derived are identical to those stated above Analysis of carotid derived PEPs versus dDEN/dt derived PEPs showed the following results

Posture Series r = +0.98 ($p < 0.001$)
slope = 1.02 msec/msec
intercept = 4.02 msec
Control for IHG r = +0.91 ($p < 0.001$)
slope = 1.02 msec/msec
intercept = 3.44 msec
IHG r = +0.82 ($p < 0.001$)
slope = 0.72 msec/msec
intercept = 38.36 msec

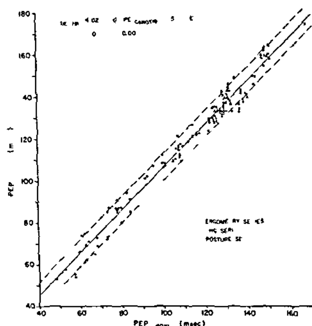


Fig 3 Correlation of pre-ejection period (PEP) from carotid curve (PEP ...) with PEP from densitogram derivative curve (PEP ...) r = +0.98 $p < 0.001$

Controls for
bicycle ergometry
r = +0.93 ($p < 0.001$)
slope = 1.09 msec/msec
intercept = −2.51 msec
Bicycle ergometry
r = +0.89 ($p < 0.001$)
slope = 1.01 msec/msec
intercept = 5.73 msec
Recovery from
bicycle ergometry
r = +0.97 ($p < 0.001$)
slope = 1.01 msec/msec
intercept = 5.73 msec
Over all analysis of
all data above
r = +0.98 ($p < 0.001$)
slope = 1.02 msec/msec
intercept = 4.02 msec

Discussion

The comparisons of carotid derived LVETs versus dDEN/dt derived LVETs and carotid derived PEPs versus dDEN/dt derived PEPs all showed highly statistically significant correlation coefficients ($p < 0.001$ for all comparisons made) with slopes displaying the very close tracking

among the two methods A perfect correlation with a slope of one on a linear regression would yield an intercept of zero Most intercepts for these data showed only a few milliseconds deviation from zero (i e , ± 5 msec or less) but in a few cases the deviation was greater (eg , 38 36 msec for IHG) The importance of the intercepts must be taken in context, however, since by definition the intercepts reported reflect the intersection of the respective slopes at zero LVET carotid and zero PEP carotid i e , theoretical points which do not occur in practice Thus intercepts reported which do deviate more from zero reflect either a slightly steeper or more flat slope for those challenges but do not reflect the absolute difference expected among the two methods for determining the LVET or PEP Figs 2 and 3 show this to be the case wherein no points for any challenge show large discrepancies among the two methods for determining LVET and PEP

In conclusion the close tracking among LVETs and PEPs for carotid versus dDEN/dt curves under the newly studied challenges support the validity of dDEN/dt as a valid and reliable pulse measurement in determining all the STI under technically difficult conditions

Summary

Systolic time intervals were determined in 10 volunteer subjects at rest and during a variety of cardiocirculatory stresses to further evaluate the ear densitogram derivative as a replacement for the carotid pulse curve There was close tracking of the two methods not only for left ventricular ejection time (r = +0 98) but also for pre ejection period (r = +0 98) The results confirmed that this technically simple and remarkably stable wave form permits reliable measurement of the systolic time intervals both at rest and during the actual performance of stress

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The thoracic windows for electrical ventricular defibrillation current

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P G Wilcox B S Ch E
W A Tacker Jr M D Ph D
West Lafayette Ind

A considerable controversy still exists regarding the optimum location and size of electrodes to achieve ventricular defibrillation with the mini mum delivered energy and current irrespective of the type of electrical current waveform employed Although several studies have been carried out seeking to identify the optimum electrode place ment [1-3] the evidence adduced to date is inade quate to show that the combination of one size and location is superior to another In order to investigate this subject in a quantitative manner studies were carried out using dogs to map out the relative defibrillation threshold current levels with transchest and chest to back electrodes The results of this investigation which are the subject of this paper indicate that there are well defined areas on the precordial chest wall where current gains easy access to the heart these areas we have referred to as the thoracic windows for ventric ular defibrillation current

Methods and materials

The studies were carried out using 14 dogs ranging in weight from 5 4 Kg to 18 5 Kg and anesthetized with intravenously administered sodium pentobarbital (30 mg /Kg) All animals were intubated to provide a patent airway Femoral artery blood pressure and Lead III ECG were recorded using the Physiograph Ventric ular fibrillation was induced using a bipolar cath eter electrode placed in the right ventricle via the right jugular vein

Three series of defibrillation studies were conducted using a small circular precordial ex ploring electrode paired with a large fixed position electrode The electrodes were placed in a transchest configuration in the first two studies and in a chest to back configuration in the third Using 4 to 5 msec damped sinusoidal shocks the lowest (threshold) values of current which would defibrillate were determined in each animal The entire precordial chest wall was explored with the small electrode to compose isodose current defi brillation contour maps Isodose lines were drawn according to values for peak amperes/Kg of body weight

In the first study the exploring electrode (3 2 cm diameter) was sutured to various sites on the shaved left hemithorax The larger (fixed) circular electrode (12 cm diameter) was sutured to the shaved right hemithorax Both electrodes were coated with low resistivity (5 5 ohm cm) electrode paste A grid was drawn on the left chest wall and the exploring electrode was placed successively on grid points at 1 6 cm intervals along intercostal spaces The area explored amounted to 80 per cent of the left thorax Threshold defibrillation current was determined in a manner previously described by us for each exploring electrode position Special care was taken to remove the electrode paste from the skin when the exploring electrode placement was changed

Following determination of the thresholds on the left hemithorax the large (12 cm) fixed electrode was moved to the left chest wall and sutured with its center at the level of the apex

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Methods and materials

The studies were carried out using 14 dogs ranging in weight from 5.4 Kg to 18.5 Kg and anesthetized with intravenously administered sodium pentobarbital (30 mg/Kg). All animals were intubated to provide a patent airway. Femoral artery blood pressure and Lead III ECG were recorded using the Physiograph. Ventricular fibrillation was induced using a bipolar catheter electrode placed in the right ventricle via the right jugular vein.

Three series of defibrillation studies were conducted using a small circular precordial exploring electrode paired with a large fixed position electrode. The electrodes were placed in a transchest configuration in the first two studies and in a chest to back configuration in the third. Using 4 to 5 msec damped sinusoidal shocks the lowest (threshold) values of current which would defibrillate were determined in each animal. The entire precordial chest wall was explored with the small electrode to compose isodose current defibrillation contour maps. Isodose lines were drawn according to values for peak amperes/Kg of body weight.

In the first study the exploring electrode (3.2 cm diameter) was sutured to various sites on the shaved left hemithorax. The larger (fixed) circular electrode (12 cm diameter) was sutured to the shaved right hemithorax. Both electrodes were coated with low resistivity (5.5 ohm cm) electrode paste. A grid was drawn on the left chest wall and the exploring electrode was placed successively on grid points at 1.6 cm intervals along intercostal spaces. The area explored amounted to 80 per cent of the left thorax. Threshold defibrillation current was determined in a manner previously described by us[4] for each exploring electrode position. Special care was taken to remove the electrode paste from the skin when the exploring electrode placement was changed.

Following determination of the thresholds on the left hemithorax the large (12 cm) fixed electrode was moved to the left chest wall and sutured with its center at the level of the apex

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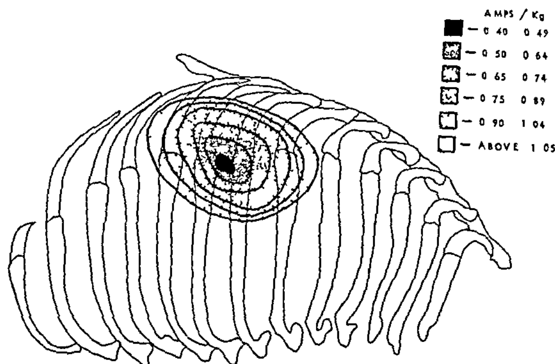


Fig 1A Isodose current map expressed in amps per kilogram of body weight for defibrillation with the small (3 2 cm diameter) exploring electrode located at various sites on the left chest the reference electrode (12 cm diameter) was applied to the right chest

beat A grid was drawn on the right chest wall and defibrillation current thresholds were determined at points 1 6 cm apart

From the threshold currents for defibrillation with the small electrode placements on the various sites of the left and right sides of the thorax, threshold isodose defibrillation contour (amps/Kg) maps were plotted to delineate those areas where lesser and greater current doses were required for defibrillation

The third series employed a large wire screen electrode (23 by 30 cm) on the back paired with the 3 2 cm electrode placed at different locations on the precordial chest wall The reference screen electrode was applied to the shaved dorsal surface of the animal following application of low resistivity electrode paste to the skin Defibrillation thresholds were determined with the exploring electrode (3 2 cm) sutured to multiple points spaced 1 6 cm apart on the entire ventral chest wall From these threshold current values, isodose current maps were plotted to delineate the regions where lesser and greater current dose levels are required for defibrillation with chest to back electrode placements

The defibrillator employed* provided a damped sine wave of current of 4 to 5 msec in duration In every defibrillation trial the voltage across and the current through the electrodes were measured using a two channel memory oscilloscope * The current was determined by measuring the voltage across an 0 2 ohm resistor placed in series with the defibrillator and subject

The general plan used to determine a threshold current for each electrode position consisted of precipitating fibrillation by applying 2 msec rectangular wave pulses having a frequency of 60 Hz and a potential of 5 volts to the catheter electrode in the right ventricle Fibrillation was confirmed by noting replacement of the QRS T complexes in the ECG by fibrillation waves and by recording a loss of blood pressure Immediately after fibrillation was confirmed the defibrillation threshold determinations were begun An energy setting based on our past experience [6] was chosen and defibrillation was attempted If this level of current defibrillated the procedure was repeated employing 5 per cent less current If defibrillation did not occur on the first trial defibrillation was achieved with an energy setting known from past experience to be capable of defibrillation All threshold currents were evaluated on the success or failure of the first shock which was administered within 15 seconds after inducing fibrillation This procedure was repeated until the threshold current for defibrillation of that subject was

Model 09?00 Phy io Control Redmond Wash

Model D 15 Tektronix Portland Ore

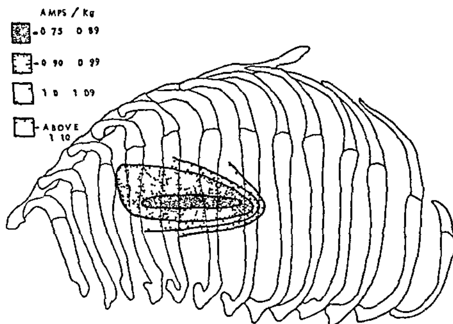


Fig 1B Isodose current map expressed in amps per kilogram of body weight for defibrillation with the small electrode (3 2 cm diameter) located at various sites on the right chest the reference electrode (1? cm diameter) was applied to the left chest

established The threshold was therefore identified as a current 5 per cent higher than the highest level that failed to defibrillate On the average 400 fibrillation-defibrillation trials were performed for 40 exploring electrode positions on each animal

Results

Fig 1A presents an isodose contour map of the left hemithorax of a typical dog using the large right thoracic electrode paired with the small exploring electrode on the left thorax Fig 1B presents the corresponding isodose contour map for the right hemithorax using the large electrode applied to the left thorax and paired with the small exploring electrode on the right hemithorax From these maps it can be seen that the lowest threshold current dose (0 40 to 0 49 amps/Kg) was found when the small active electrode was on the left thorax over the apex beat area Thus there appears to be one electrical window on the left hemithorax with this transchest electrode array On the right hemithorax (Fig 1B) there is a linear region for the window and the lowest current dose is slightly higher (0 75 to 0 89 amps/Kg)

Fig 2A presents the isodose contour map obtained with the small circular electrode applied to different sites on the ventral chest wall when the large screen electrode was applied to the back Fig 2B presents the isodose map for the same animal with the large circular reference electrode on the right thorax and the small exploring electrode on the left thorax With the chest to back array it can be seen that the lowest threshold current for defibrillation (0 6 to 0 69 amps/Kg) was obtained when the small electrode was slightly anterior to the apex-beat area With the transchest electrode array the same minimum current was required for the exploring electrode over the apex beat area

Discussion

The data presented in Figs 1 and 2 are for two typical animals the results obtained on the other animals were remarkably similar This similarity within each group is probably due to our presentation of data in terms of the current dose—that is normalization of the threshold current for defibrillation by division by the animal s body weight In a previous paper we have shown that this technique minimizes the effect of variations in body weight and species differences

Of paramount importance in studies which involve optimization of electrode position is the stability of the defibrillation threshold over

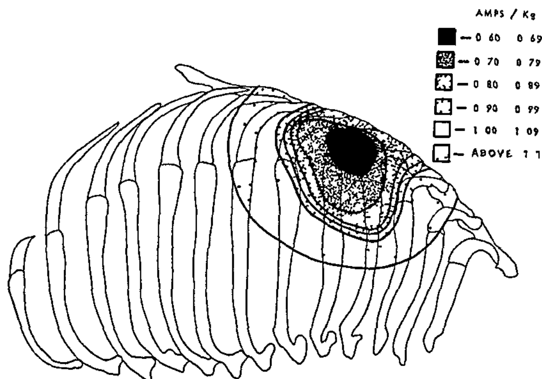


Fig 2A Isodose current map expressed in amps per kilogram of body weight for defibrillation with the small (3 2 cm diameter) electrode located at various sites on the chest the reference electrode (23 × 30 cm screen) was applied to the back

prolonged periods In studies carried out by the authors[7 8] control threshold currents determined every fifteen minutes over one hour periods were within a ten per cent range In studies to be reported soon, the threshold values were determined over an eight hour period and the same degree of stability of threshold was encountered In this latter series a considerable number of countershocks was given to each animal and no cumulative effect on threshold was observed

The optimum location for thoracic defibrillating electrodes is by no means a settled matter Kouwenhoven and associates[1] in a series of studies in dogs, contrived an ingenious experiment to discover the location for thoracic electrodes to obtain the maximum current through the heart In order to detect the cardiac current they placed the heart in the center of a current transformer and closed the chest Sixty Hz alternating current was applied to electrodes placed at different sites on the thorax The maximum current flow through the heart was obtained with one electrode over the suprasternal notch and the other at the level of the xiphoid process along a midclavicular line Using dogs in their early DC defibrillation studies Lown and colleagues reported that the least energy required for defibrillation was encountered with one electrode placed over the area of the 'apex thrust and the other placed on the opposite side of the thorax at the same level In his first studies in man Lown and co workers[3] advocated locating one electrode over the fifth intercostal space on the left with the other electrode to the right of the sternum at about the second intercostal space Later Lown[4] reported that a better site for the left electrode was the left infrascapular area, i e , the chest to back electrode array was introduced However, it is unclear whether this array optimizes both atrial and ventricular defibrillation

It is clear from these studies that there are optimum locations for the left thoracic electrode With either a transchest or chest to back placement the electrode on the left chest should be placed over the apex beat area In the study shown in Fig 2 the same animal was used for transchest and chest to back determinations The lowest current dose for this animal with the precordial electrode array was 0 6 amps/Kg This was obtained with the small electrode placed over the apex beat area and the large circular electrode on the right thorax With the chest to back placement the lowest current dose was 0 6 amps/Kg this value was obtained with the small electrode

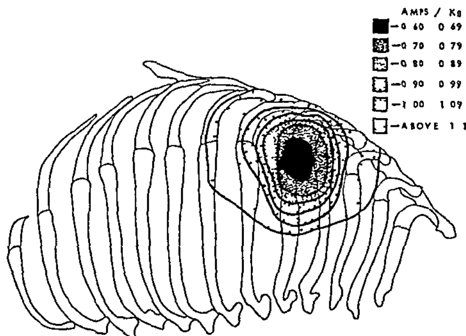


Fig. 2B. Isodose current map expressed in amps per kilogram of body weight for defibrillation with the small (3.2 cm diameter) electrode applied to various sites on the left thorax; the reference electrode (12 cm diameter) was applied to the right chest. The contour maps in Figs. *2A* and *2B* were obtained on the same animal.

placed slightly anterior to the apex-beat area and the large screen electrode placed on the dorsal thorax. The similarity of these two current dose levels indicates that it is important to locate one electrode in the vicinity of the apex beat area. Among all of the animals in this study, the current dose levels obtained with transchest electrodes ranged from 0.35 to 0.82 amps per kilogram. With the chest to back array, the lowest dose levels ranged from 0.46 to 0.97 amps/Kg. These values are slightly lower than those obtained with electrodes of various sizes applied to the chests of animals ranging from 2 to 340 Kg.[4]

It is important to note that the present study does not identify the correct size of electrodes to be used; rather it serves as a guide to indicate that one electrode should be placed over the apex beat area. Very few studies have been carried out which indicate that there is an optimum electrode size with which defibrillation can be achieved using the least current dose. Ewy has reported that in dogs, the use of a pair of very small transthoracic electrodes requires a high current dose. The dose required decreases as the electrodes are made larger, up to a point, but then increases again as the electrodes are made very large. We have verified this finding (unpublished data). Although difficult to quantitate, this observation is easy to explain on the basis of current distribution. With very small transthoracic electrodes, a high level defibrillating current must be used to obtain an adequate amount of current through the periphery of the ventricles. With the optimum diameter electrodes (in relation to chest size), a larger percentage of the injected current flows through the ventricles. In addition, the distribution of current is more even. With very large electrodes, a smaller percentage of the injected current passes through the heart; hence the total current will be high. Thus, it is logical to expect that there is an optimum size of electrodes for a given subject and that the optimum electrode size will increase with increased subject size. Determination of appropriate size for humans awaits further investigation. Location of "windows" on the human chest also requires further research.

Summary

The thoraces of dogs were mapped out to identify those areas where defibrillating current gains easiest access to the heart. Of all of the transchest and chest to back electrode locations

the lowest current dose (0 6 amp per kilogram of body weight) was found with one electrode over the apex-beat area with transchest electrodes and slightly anterior to the apex-beat area with chest to back electrodes

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Pulmonary and left atrial hemodynamics in mitral stenosis

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The relationship between mitral stenosis and pulmonary artery hypertension is not well under stood A linear relationship does not exist between the left atrial pressure and valve orifice or between left atrial pressure and pulmonary artery pressure It is known that atrial and pulmonary compliance influence atrial and pulmonary hemodynamics To gain insight into these relationships the following experiment was performed

Method

A circuit was constructed of rigid plastic tubing (Tygon) and filled with normal saline (Fig 1) A nonsucking continuous inflow intermittent out flow pump was used to mimic the right heart Silicone rubber latex and plastic atria of three different compliances were evaluated Volume pressure curves were constructed for each atrium (Fig 2) A simulated lung allowed independent control of pulmonary vascular resistance and compliance Pulmonary vascular resistance was arbitrarily set at a physiologic level (pulmonary artery pressure of 22/10) using a flow rate of 7 L / min and a 3 0 cm valve orifice by placing a suitable number of wire screens in the lung model to achieve the desired resistance which was not altered during the experiments Pulmonary vascular compliance was controlled at four levels by varying the amount of air in the buffer chamber of the model lung (Fig 3) An inter changeable disk placed proximal to the Bjork Shiley* atrioventricular valve allowed control of orifice size at 3 0 1 0 0 75 0 5 or 0 25 cm ² (Fig 1) A reservoir simulated the additional blood avail able to the human circulation by venous constric tion during exercise Venous pressure was controlled at 10 mm Hg to simulate a resting state or 20 mm Hg to mimic an exercise state Flow through the circuit (cardiac output) was measured with an electromagnetic flow probe which was calibrated by timed collection of saline using a similar circuit Pressures were measured in the atrium (mean) and pulmonary artery (pulsatile and mean) using Statham strain gauges and a Gould direct writing recorder

Data were collected at two heart rates (54 and 81 beats/min) for each of three atria using five valve orifices four pulmonary compliances and two venous pressures (10 and 20 mm Hg) At the onset of each experiment venous pressure was adjusted to the desired level using the reservoir The pump was actuated and venous pressure was allowed to find its own level with the reservoir excluded When a stable state was achieved (usually by one minute) pressures and flow were recorded and a new experiment begun

Results

The experimental data are presented in Tables I to IV These data were examined by analysis of variance and significance determined by the F test as summarized in Tables V and VI

At a heart rate of 81 beats/min cardiac output is related to atrial compliance ($p < 005$) valve

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*Shiley Laboratories, I c Santa Ana Calif

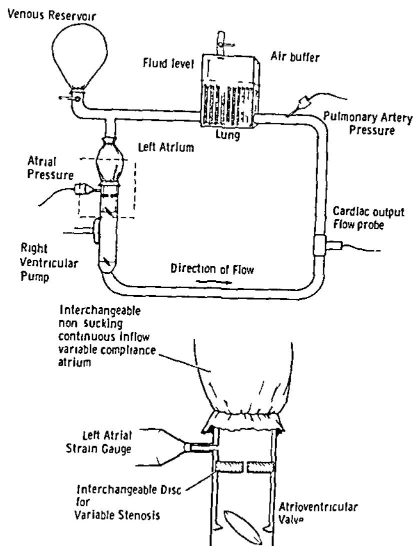


Fig 1 Experimental scheme of the right ventricle lung and left atrium

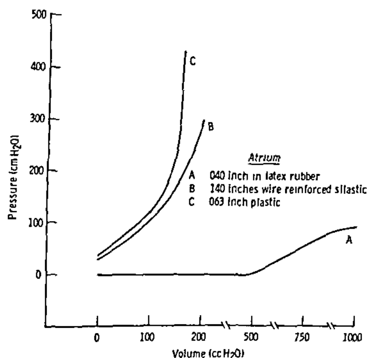


Fig 2 Volume-pressure compliance curves of these experimental atria

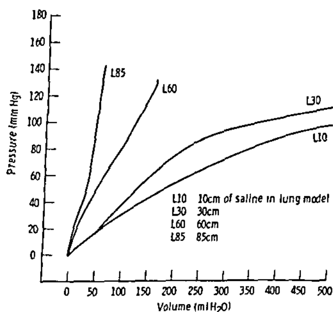


Fig 3 Volume-pressure compliance curves of the lung model at the four experimental levels

Table I Raw data for atrium A—rate 81 beats/min

Valve orifice area	Pulmonary compliance (% of chamber fluid filled)	Venous reservoir pressure (mm Hg)	Mean left atrial pressure (mm Hg)	Mean pulmonary artery pressure (mm Hg)	Cardiac output (liters/min)
3.00 cm	10	10	8	17	7 0
	10	20	18	26	7 0
	30	10	8	17	6 6
	30	20	18	26	6 7
	60	10	7	62	⁻5
	60	20	15	73	7 5
	85	10	9	100	7 8
	85	?0	18	124	8 2
1 00 cm	10	10	15	23	5 6
	10	20	23	29	6 2
	30	10	16	21	6 0
	30	20	27	3?	6 4
	60	10	13	⁻0	6 ɔ
	60	20	23	89	6 4
	85	10	15	1?4	6 9
	85	20	25	150	6 6
0 7ɔ cm.	10	10	28	33	6.0
	10	20	30	36	6 0
	30	10	27	33	5 6
	30	20	3?	38	6 0
	60	10	25	90	6 0
	60	20	31	98	6 3
	85	10	27	148	6 J
	85	20	32	172	6 4
0 50 cm	10	10	45	52	5 5
	10	?0	44	50	5 0
	30	10	42	50	5 3
	30	20	44	53	5 3
	60	10	45	124	5 8
	60	20	52	134	5 9
	85	10	40	174	5 8
	85	20	48	184	5 ⁻
0 25 cm	10	10	44	32	2 0
	10	20	58	47	2 3
	30	10	54	37	2.2
	30	20	57	60	2 4
	60	10	60	144	2.8
	60	20	65	150	2 9
	8ɔ	10	64	158	2 9
	85	20	65	160	2.9

orifice (p < 005) and pulmonary compliance (p < 005) in that order of importance and venous pressure is not significant (Table V) Mean atrial pressure is related to valve orifice (p < 005) atrial compliance (p < 005) pulmonary compliance (p < 005) and venous pressure (p < 005) in decreasing order of importance Mean pulmonary artery pressure is also related to orifice size (p < 00ɔ) pulmonary compliance (p < 00ɔ) venous pressure (p < 005) and atrial compliance (p < 01) in order of significance

The interaction between atrial compliance and pulmonary compliance significantly influences mean atrial pressure (p < 005) mean pulmonary artery pressure (p < 005) and cardiac output (p < 00ɔ) in that order (Table V) Similarly the interaction of atrial compliance and valve orifice influences cardiac output (p < 00ɔ) mean pulmonary artery pressure (p < 005) and atrial pressure (p < 00ɔ) The interaction of pulmo

Table II Raw data for atrium B—rate 81 beats/min

Valve orifice area	*Pulmonary compliance (% of chamber fluid filled)*	*Venous reservoir pressure (mm Hg)*	*Mean left atrial pressure (mm Hg)*	*Mean pulmonary artery pressure (mm Hg)*	*Cardiac output (liters/min)*
3.00 cm²	10	10	9	27	6.3
	10	20	15	34	6.2
	30	10	8	27	6.5
	30	20	18	37	6.4
	60	10	8	64	7.0
	60	20	16	80	7.0
	85	10	18	86	7.5
	85	20	27	114	7.5
1.00 cm	10	10	18	28	6.2
	10	20	24	34	6.2
	30	10	19	28	6.2
	30	20	25	34	6.5
	60	10	21	68	6.6
	60	20	28	89	6.5
	85	10	26	94	7.0
	85	20	38	120	6.6
0.75 cm	10	10	28	37	6.2
	10	20	36	45	6.4
	30	10	30	35	5.8
	30	20	38	47	6.0
	60	10	35	108	6.4
	60	20	44	134	6.2
	85	10	36	116	6.5
	85	20	55	144	6.4
0.50 cm²	10	10	56	67	5.9
	10	20	60	67	5.7
	30	10	55	67	5.6
	30	20	58	65	6.0
	60	10	54	128	6.0
	60	20	58	132	6.1
	85	10	58	138	6.0
	85	20	65	154	6.2
0.25 cm²*	10	10	145	152	3.3
	10	20	185	207	4.0
	30	10	180	202	4.0

*Further data not recorded because of high pressure

nary compliance and valve orifice have a smaller but significant effect on pulmonary ($p < .005$) and atrial pressure ($p < .05$). The remaining interactions (atrial compliance–venous pressure, pulmonary compliance–venous pressure, venous pressure–valve orifice) as shown in Table V are not significant.

At a heart rate of 54 beats/min, valve orifice is the only significant variable and affects cardiac output ($p < .005$), pulmonary artery pressure ($p < .005$), and atrial pressure ($p < .005$), in that order of importance (Table VI). The interaction of orifice with venous pressure ($p < .01$) and atrial compliance with valve orifice ($p < .05$) had a significant effect on cardiac output.

Discussion

Adequate filling of the left ventricle through a stenotic mitral valve requires increased left atrial pressure. To maintain gradient flow, an increased pressure in the pulmonary venous system is necessary. Similarly, the pulmonary artery pressure must rise. Secondary changes, both obliterative and reactive vasoconstriction, then occur in the pulmonary vascular bed causing the pulmonary artery pressure to increase beyond that necessitated by gradients only.[1] Eventual limitation of cardiac output effected by valvar orifice and pressure limits is frequently accompanied by a further decrease with exercise.

We have used an artificial circuit to examine

Table III Raw data for atrium C—rate 81 beats/min

Valve orifice area	*Pulmonary compliance (% of chamber fluid filled)*	*Venous reservoir pressure (mm Hg)*	*Mean left atrial pressure (mm Hg)*	*Mean pulmonary artery pressure (mm Hg)*	*Cardiac output (liters/min)*
3 00 cm	10	10	4	24	6 5
	10	20	13	32	6 6
	30	10	5	27	6 7
	30	20	12	31	6 7
1 00 cm	10	10	16	29	6 4
	10	20	21	31	6 5
	30	10	16	30	6 5
	30	20	21	33	6 5
0 5 cm.	10	10	32	38	6 4
	10	20	30	39	6 4
	30	10	34	41	6 3
	30	20	36	43	6 4
0 50 cm	10	10	54	61	6 1
	10	20	58	63	6 0
	30	10	56	63	6 0
	30	20	60	64	6 2
0 25 cm	10	10	145	159	3 4
	10	20	190	194	4 2
	30	10	185	194	4 2
	30	20	190	200	4 5

left atrial and pulmonary hemodynamics as influenced by atrial and pulmonary compliance mitral valve orifice heart rate venous pressure and the influence of these variables on cardiac output The output of the right ventricular pump is determined by the inflow with the result that pooling of blood in the lung and atrium resulted in decreased venous return and cardiac output The lung model was designed with a fixed pulmonary vascular resistance to give a normal phasic pulmonary artery pressure and a variable compliance Patients with mitral stenosis may have normal pulmonary resistance and compliance or fixed increase in pulmonary resistance and decreased compliance The artificial atria lacked the ability to contract and therefore could provide only two functions of the normal atrium (conduit and reservoir) Although atrial systole contributes significantly to ventricular filling in the normal heart its contribution in the face of mitral stenosis is negligible[8]

Within these limitations our model represents an effort to provide data which are not clinically available on the influence of pulmonary and atrial compliance on pulmonary and atrial hemodynamics in mitral stenosis

We found left atrial pressure to be most directly related to mitral orifice but also significantly to atrial compliance pulmonary compliance systemic venous pressure and the interactions of atrial compliance-orifice atrial compliance-pulmonary compliance and pulmonary compliance-valve orifice The complexity of these interactions indicates why a simple linear relationship has not been found between orifice size in mitral stenosis and left atrial pressure[5] between orifice size and pulmonary artery pressure[8] or between atrial pressure and volume

In contrast to valve orifice which has been frequently measured atrial compliance is seldom determined and those factors responsible for alteration of atrial compliance in mitral stenosis are poorly understood[9,1] Grant and associates[1] have emphasized the reservoir function of the left atrium which stores blood (42 per cent of left ventricular stroke volume) and energy while the mitral valve is closed and the conduit function of the atrium when the valve is open The atrium functions in this way whether it is beating or fibrillating as atrial systole contributes little to ventricular filling in mitral stenosis In our model atrial compliance was the most significant determinant of cardiac output at a heart rate of 81 beats/min

Table IV Raw data for atria A, B, C—rate 54 beats/min

Valve orifice area	*Pulmonary compliance (% of chamber fluid filled)*	*Venous reservoir pressure (mm Hg)*	*Mean left atrial pressure (mm Hg)*	*Mean pulmonary artery pressure (mm Hg)*	*Cardiac output (liters/min)*
Atrium A					
3 00 cm^2	10	10	7	27	6 0
	10	20	24	32	6 2
1 00 cm^2	10	10	14	31	4 5
	10	20	21	32	5 0
0 75 cm^2	10	10	19	30	4 6
	10	20	24	32	4 8
0 50 cm	10	10	23	31	4 2
	10	20	28	36	4 4
0 25 cm^2	10	10	64	91	2 4
	10	20	—	—	—
Atrium B					
3 00 cm^2	10	10	3	30	4 6
	10	20	9	33	4 6
1 00 cm	10	10	13	35	4 6
	10	20	18	35	4 7
0 75 cm^2	10	10	15	33	4 4
	10	20	32	40	4 4
0 50 cm	10	10	26	35	4 2
	10	20	32	40	4 4
0 25 cm	10	10	130	105	2 9
	10	20	110	103	2 5
Atrium C					
3 00 cm	10	10	10	31	4 6
	10	20	14	35	4 6
1 00 cm^2	10	10	15	29	4 6
	10	20	12	41	4 8
0 75 cm^2	10	10	19	31	4 6
	10	20	26	41	4 7
0 50 cm	10	10	29	49	4 4
	10	20	37	61	4 4
0 25 cm^2	10	10	—	—	2 7
	10	20	—	—	—

We observed pulmonary artery pressure to be influenced by valve orifice pulmonary compliance venous pressure, atrial compliance and the interaction of atrial compliance-valve orifice atrial compliance-pulmonary compliance and pulmonary compliance-valve orifice in decreasing importance The complexity of these interactions is compounded clinically by alterations in pulmonary vascular resistance which may be anatomic and fixed or physiologic and variable [11-13]

We found that cardiac output was influenced by atrial compliance valve orifice the interaction of atrial and pulmonary compliance, pulmonary compliance, and the interaction of atrial compliance-valve orifice, in decreasing order of significance The influence of atrial compliance on cardiac output in the absence of mitral stenosis has previously been demonstrated [14]

Heart rate was such a significant variable that when it was reduced from 81 to 54 beats/min, only the most compliant lung model could be used without pressures rising to unphysiologic levels and as valve orifice was decreased pressures did become unphysiologic These observations serve to emphasize the role of atrial and pulmonary compliance at a physiologic heart rate When bradycardia occurs and cardiac output is maintained the increased stroke volume exceeds the compliance limitations of the lung and atrium and pressures rise inordinately In this non compliant setting cardiac output is determined primarily by valve orifice and also by

Table V Summary of analysis of variance (F test values) Heart rate 81 beats/min

Variables	Cardiac output	Parameters: Mean left atrial pressure	Parameters: Mean pulmonary artery pressure
Atria A B C	164 05	104 54	21 07
Pulmonary compliance	66 53	13 90	153 21
Valve orifices	107.30	333 50	241.56
Venous pressure	0 003	8 98	15.33
Interactions			
Atria/pulmonary compliance	82 99	6 17	7 97
Atria/valve orifices	12.97	44 03	36 94
Atria/venous pressure	0 39	0 09	0.25
Pulmonary compliance/valve orifices	0 24	2 44	4 81
Pulmonary compliance/venous pressure	0 13	0 13	0 19
Venous pressure/valve orifices	0 08	0 12	0 34

p ≤ 0 005
p ≤ 0 010
p ≤ 0 050.

Table VI Summary of analysis of variance (F test values) Heart rate 54 beats/min

Variables	Cardiac output	Parameters: Mean left atrial pressure	Parameters: Mean pulmonary artery pressure
Atria A B C	1 17	1 30	3 47
Venous pressure	2 73	1 74	2.20
Valve orifices	64 46	30 09	37 12
Interactions			
Atria/venous pressure	0 86	1 22	0 8?
Atria/valve orifices	4 06	1 04	2 01
Valve orifices/venous pressure	7 10	0 46	0 66

p ≤ 0 005
p ≤ 0 010
p ≤ 0 050.

the interaction of valve orifice–venous pressure and atrial compliance–valve orifice

This study serves to emphasize the role of atrial and pulmonary compliance in modulating atrial and pulmonary hemodynamics in mitral stenosis Existing clinical data indicates the frequently poor correlation between orifice size and these commonly obtained hemodynamic measurements In addition to the recognized variable response of the pulmonary resistance vessels (arterioles) to the pressure alterations of the stenotic mitral valve the alterations in compliance of the atrium and pulmonary vasculature must be considered Our understanding of the role of the compliance of these two vascular compartments is limited by the lack of clinical measurements and a poor understanding of the degree to which pathologic changes alter normal compliance Does atrial muscle hypertrophy decrease or enhance compliance? Does pulmonary hypertension and secondary dilatation of the major pulmonary arteries diminish or augment compliance of these arteries? A better understanding of the hemodynamic alterations of mitral stenosis will result when compliance can be more accurately evaluated

Summary

A laboratory model has been utilized to evaluate left atrial and pulmonary hemodynamics while comparing atria of three different compliances five valve orifices four pulmonary compliances two venous pressures and a predetermined pulmonary vascular resistance The data demonstrate significant relationships between these variables and cardiac output pulmonary artery pressure and left atrial pressure and between the variables themselves The complexity of these interrelationships is consistent with the lack of simple linear relations between current clinical measurements and emphasizes the need for measurements of compliance if the hemodynamic consequences of mitral stenosis are to be better understood

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Effects of propranolol on the development of renovascular hypertension in the rat

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The antihypertensive effect of propranolol in both essential and renal hypertension in man has been well documented by several investigators. The effect of propranolol has also been studied in rats with various types of experimental hypertension such as DOCA (desoxycorticosterone acetate), spontaneous, and renovascular hypertension. In some studies propranolol was reported to have a marked hypotensive effect but in others it was completely ineffective. This great variance in results may be due to the different types and/or severity and duration of the hypertension.

The present study was undertaken to investigate the effects of propranolol (Inderal) on the development of two kidney renovascular hypertension in rats (one renal artery constricted, contralateral kidney untouched). The effects of propranolol on rats with established renovascular hypertension were also investigated.

Materials and methods

Unanesthetized male Sprague Dawley rats (150 to 200 Gm.) were used. They were kept in individual cages, fed Purina chow, and had free access to tap water. Systolic blood pressure was measured by the tail-cuff method; heart rate was calculated from the pulse tracing. The rats were prewarmed in an incubator (38° C.) for 20 minutes before the recordings were made. Hypertension was induced by placing a U shaped silver clip (0.2 mm. internal gap) around the left renal artery under ether anesthesia, leaving the right kidney untouched. Only those rats which developed a systolic pressure of 160 mm. Hg or higher were considered hypertensive. Peripheral plasma renin activity (PRA) was determined by a modified technique of the radioimmunoassay method of Haber and associates, as previously described. PRA was expressed as ng. of generated angiotensin I per ml. of plasma per one hour incubation. All results in the text and figures are expressed as the mean ± SEM. Student's t test and the χ^2 test were used for statistical analysis and correlation coefficients were calculated where applicable.

Administration of propranolol during the developmental phase of renovascular hypertension. Forty rats were divided into two groups of 20 each. One group received propranolol subcutaneously (20 mg./Kg. of body weight three times a day); the propranolol powder was dissolved in a 0.2 ml. volume of 5 per cent dextrose. Treatment was started three days before clipping and was continued for four weeks after clipping. The control group received 0.2 ml. of 5 per cent dextrose solution only. Changes in body weight, systolic pressure, and heart rate were recorded daily in both groups for two days before starting treatment, on the third day after treatment (before clipping), and at weekly intervals after clipping during the treatment period. At the end of the fourth week all rats in both groups were

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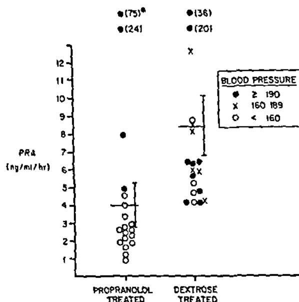


Fig 2 Plasma renin activity in propranolol treated and dextrose treated rats *Black dots* indicate rats with BP of 190 mm. H or more *X* indicates BP between 160 and 189 and *open circles* indicate BP less than 160 mm Hg *Horizontal bar* represents mean *vertical bar* represents standard error of mean *Parentheses* indicate PRA values not within the scale Number with asterisk was not considered for calculation of mean

with heart rate in both the propranolol treated rats ($r = 0440$ $p = 005$) and the dextrose treated rats ($r = 0690$ $p < 0001$)

3 *Effect on PRA* The mean PRA was 41 ± 926 ng /ml /hr in the propranolol treated group and 84 ± 17 in the dextrose treated group ($p < 0025$) It should be noted that one of the rats from the propranolol group with an extremely high PRA (75 4) was excluded from the above analysis PRA in the propranolol treated rats that became hypertensive was 281 ± 16 as compared with 242 ± 026 ($p < 0001$) in those rats that remained normotensive A great degree of overlapping was observed in the PRAs of the control rats with severe and moderate hypertension and the rats that remained normotensive (Fig 2) PRA was significantly lower ($p < 0001$) in the normotensive propranolol treated rats (2.42 ± 026) as compared with that of the normotensive control rats (559 ± 20) Systolic pressure correlated with PRA in both the propranolol treated and dextrose treated rats $r = 0442$ ($p = 005$) and $r = 0690$ ($p < 0001$) respectively

4 *Effect on heart weight* There was no significant difference in body weight between the two

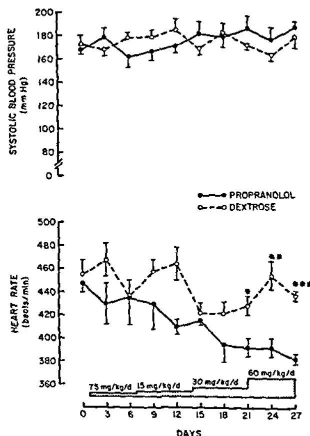


Fig 3 Mean systolic blood pressure *(top)* and mean heart rate in rats with established renal hypertension treated with propranolol *(solid line)* and controls *(broken line)* Horizontal striped bar *(bottom)* indicates treatment and doses of propranolol used

groups (300 Gm in the propranolol treated and 314 Gm in the dextrose treated) Heart weight in the propranolol treated group ($n = 19$) was 917 ± 19 mg and 1011 ± 33 in the dextrose treated group ($p < 005$) Heart weight correlated with blood pressure and PRA ($r = 069$ and 064 respectively) in the propranolol treated rats but no correlation was observed in the dextrose treated rats

Effect of propranolol in established hypertension Oral propranolol had no effect on blood pressure at any time during treatment when given after the development of hypertension even after increasing the dose to very high levels (Fig 3) At the end of treatment (fourth week) the average BP was 184 ± 6 mm Hg in the propranolol treated and 175 ± 9 mm Hg in the dextrose treated rats ($p > 005$) Heart rate was significantly lower in the propranolol treated rats only when they were given very high doses of propra

decapitated within two hours after the last injection of propranolol or dextrose Blood was collected in chilled tubes containing disodium ethylenediamine tetraacetic acid and was immediately centrifuged at 4° C for 20 minutes The plasma was stored at –20° C for subsequent determination of PRA Hearts were excised and heart weight was determined after removing the blood, great vessels, and atria

Administration of propranolol in rats with established renovascular hypertension and in normotensive rats Ten hypertensive (four weeks after clipping) and ten normotensive rats (same age and weight range) were divided into four groups of five each Five hypertensive and five normotensive rats (half of the rats in each group) were given oral propranolol three times a day via an intragastric tube, the remaining five hypertensive and five normotensive rats were used as controls and received only tap water During the first week of treatment, the dose of propranolol was 2 5 mg /Kg of body weight three times a day, during the second, third and fourth weeks, the dose was increased to 5, 10, and 20 mg /Kg three times a day, respectively Systolic pressure and heart rate were recorded at three day intervals until the end of the experiment The animals were decapitated at the end of the fourth week, and blood was collected for PRA determinations Hearts were excised and the weight was recorded

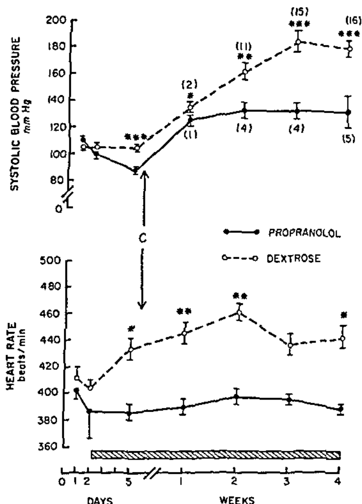


Fig 1 Mean systolic blood pressure *(top)* and mean heart rate *(bottom)* in rats treated with propranolol *(solid line)* and controls *(broken line)* Numbers in parentheses indicate number of rats with systolic pressure of 160 mm Hg or more C *(vertical arrows)* indicates point at which renal artery constriction was done Standard error of mean represented by vertical bar Horizontal hatched bar indicates treatment *p < 0 05 * p < 0 01 * p < 0 001

Results

Effect of propranolol during the developmental phase of renovascular hypertension

1 *Effect on systolic blood pressure* At the end of the fourth week, only five (25 per cent) of the propranolol treated rats were hypertensive On the other hand, sixteen (80 per cent) of the dextrose treated control rats were hypertensive This difference is highly significant ($p < 0\ 001$ χ test using Yates correction) The sequential changes in the number of rats becoming hypertensive and the changes in the average systolic pressure for each group are shown in Fig 1 The mean systolic pressure in the propranolol treated group was consistently lower during the four weeks of treatment At the end of the fourth week, the average systolic pressure was 134 ± 11 mm Hg in the propranolol group and 182 ± 7 mm Hg in the controls ($p < 0\ 001$) The five propranolol treated rats which developed hypertension after clipping had severe hypertension (BP ≥ 190), the fifteen rats that did not develop hypertension had a systolic pressure of 140 mm Hg or less The hypertension was severe in nine of the 16 hypertensive dextrose treated rats

2 *Effect of propranolol on heart rate* The changes in heart rate are also shown in Fig 1 There was no significant difference in heart rate between the two groups before treatment However on the third day of treatment (before clipping), the heart rate was significantly lower in the propranolol treated rats ($p < 0\ 05$) After clipping the heart rate was always significantly lower, with only one exception—this occurred at the end of the third week when the heart rate was lower in the propranolol treated rats, but this difference was not statistically significant ($0\ 10 < p > 0\ 05$) Systolic pressure correlated

nolol subcutaneously during the developmental phase of hypertension contradict those of Lundgren who did not succeed in modifying renovascular hypertension with propranolol although treatment was started before clipping and was continued thereafter as it was in our study. This discrepancy may be due to differences in the mode of administration and to the age and strain of rats used. Lundgren used Wistar rats and the propranolol was given orally.

Propranolol treatment did not decrease blood pressure in our study when administered orally to rats with established hypertension or to normotensive rats probably because of inadequate levels in the plasma due either to low dosage, poor absorption or both. In the treated animals lower heart rate ($p < 0.05$) occurred only at the end of the experiments with high doses of propranolol but this finding does not necessarily indicate that adequate amounts of the drug were given since the level of propranolol needed in the plasma to induce bradycardia is usually lower than that required to decrease blood pressure.

On the other hand, subcutaneous propranolol reduced both the systolic pressure and heart rate in the normotensive rats before clipping. However the mechanism(s) of this effect can only be postulated as resulting from decreased cardiac output brought about by decreased heart rate since heart rate is the main determinant of cardiac output in the normal heart. Other investigators have documented similar effects of propranolol in normotensive animals.[9]

Summary

To study the effects of beta adrenergic blockade on the development of experimental renovascular hypertension, propranolol was administered subcutaneously to 20 male Sprague Dawley rats at a dose of 20 mg/Kg of body weight three times daily. The left renal artery was constricted after three days of treatment leaving the right kidney untouched. The same procedure was performed in 20 controls which were given dextrose instead of propranolol. Treatment was continued in both groups for four weeks after constriction. At the end of the fourth week only five (25 per cent) of the propranolol treated rats developed hypertension (systolic pressure 160 mm Hg or higher) as compared to 16 (80 per cent) in the control group ($p < 0.001$). The five rats that developed hypertension in the propranolol group had severe hypertension (BP $\geq$ 190 mm Hg) and high plasma renin activity. The average systolic pressure for the propranolol treated group (hypertensive and normotensive) was 134 ± 11 and 182 ± 7 in the control group ($p < 0.001$). Heart rate was significantly lower in the propranolol group than in the controls (388 ± 4 vs 445 ± 9 beats/min, $p < 0.001$). Plasma renin activity was lower in the propranolol treated rats than in the controls (4.0 ± 1.2 and 8.2 ± 1.6 ng/ml/hr respectively, $p < 0.05$). There was no difference in body weight between the two groups. Heart weight was lower in the propranolol treated rats when compared with the controls (917 ± 18 and 1012 ± 30 mg, respectively, $p < 0.025$). A third group of rats received propranolol after clipping when renovascular hypertension had been well established. No significant decrease in blood pressure or peripheral renin activity was observed in this group although heart rate was significantly decreased ($p < 0.05$).

Our results indicate that established renovascular hypertension in rats is not affected by beta adrenergic blockade. Propranolol, however, decreases the incidence of development of hypertension in rats when administered prior to and for four weeks after renal artery constriction.

We are grateful to Ayerst Laboratories for their generous supply of propranolol.

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nolol (Fig 3) PRA was 4.85 ± 1.93 ng/ml/hr in the propranolol treated and 5.62 ± 2.10 in the dextrose treated rats, but the difference was not significant There was no significant difference in heart weight between these two groups

Effect of propranolol in normotensive rats Blood pressure in the normotensive propranolol treated and control rats at the end of the fourth week was 118 ± 8 and 114 ± 5 mm Hg, respectively ($p < 0.05$) Heart rate was significantly lower in the propranolol group (369 ± 15 beats/min) than in the dextrose group (436 ± 6 beats/min) ($p < 0.05$) PRA was lower in the propranolol treated (1.43 ± 0.4 ng/ml/hr) than in the dextrose treated group (2.27 ± 0.4), but the difference was not significant ($p > 0.05$)

Discussion

Propranolol treatment, when started prior to renal artery constriction and continued for four weeks afterward, decreased the incidence of renovascular hypertension in our study The antihypertensive effect of propranolol may be related to the mechanism by which renal artery constriction produces hypertension, it may also be a pharmacological effect not related to the pathogenesis of hypertension, or it may be a combination of both The role of renin in the development and maintenance of elevated blood pressure in the early stage of two kidney renovascular hypertension is supported by the work of many investigators[14-16] although some contradictory results have been reported[17,18] It is also well established that stimulation of the sympathetic nervous system can produce renin release and that beta blockers can prevent or alter this release[1] It is then reasonable to postulate that propranolol prevents the development of hypertension by inhibiting renin release yet one drawback to this line of reasoning is that renal artery constriction produces renin release by decreasing renal blood pressure or flow and not by sympathetic stimulation[19] Therefore it is not clear how propranolol inhibits renin release after renal artery constriction One possibility is that the sympathetic nervous system facilitates renin release when stimuli are applied that do not act through the sympathetic nervous system This possibility is supported by experiments in dogs with denervated kidneys (auto transplanted) which show that although plasma renin activity increases during a period of salt restriction, this increase is less than in control dogs with enervated kidneys[9]

It has been shown that increased cardiac output participates in the development of renal hypertension[1,2] The mechanism by which renal artery constriction produces the increase in cardiac output is not well established although it could be mediated partly through the effect of angiotensin on the central nervous system, by catecholamine release or uptake, through direct venous constriction[3] and/or through direct effect on myocardial contractility[4] It is well known that propranolol decreases heart rate and cardiac output through its beta effect Thus, it may be that propranolol exerts its antihypertensive effect in the developmental phase of renovascular hypertension by blocking an increase of cardiac output Another possibility is that propranolol prevents the development of hypertension by acting on the central nervous system, this effect may or may not be related to its beta blocking activity[5]

It is interesting to note that five rats developed hypertension despite continuous treatment with propranolol, and all five had severe hypertension (BP ≥ 190) Four of these rats also had high PRAs when compared with the rats that remained normotensive (Plasma renin was not measured in the fifth rat due to technical error) The five hypertensive rats had significantly lower heart rates (406 ± 13) than the dextrose treated rats with severe hypertension (464 ± 13) ($p < 0.01$) The heart rates of the propranolol treated rats that did not develop hypertension were not statistically different from those of the rats which developed hypertension after propranolol treatment ($p > 0.05$) This indicates that the failure of propranolol to prevent the development of hypertension in five of the rats was not due to an absence of beta blockade One possible explanation is that these five rats had more severe renal artery constrictions, despite care being taken to use only clips with the same internal dimensions (determined under microscope) Differences in the size of the renal artery could have resulted in varying degrees of renal ischemia More severe constriction of the renal artery in some of the rats may have overcome the inhibitory effect of propranolol on renin release and hypertension may have developed as a consequence of this increased renin release[16,17]

Our results obtained by administering propra

Measurements of right ventricular volumes in man from single plane cineangiograms *

A comparison to the biplane approach

Jack Ferlinz M D **
Long Beach and Irvine Calif

Angiographic determinations of ventricular volumes have classically involved the analysis of the biplane ventriculograms[1-3] A majority of cardiac catheterization laboratories however do not possess a biplane capability It is at least partially for this reason that various investigators in the field began to explore the methodology which would enable the angiographic assessment of ventricular volumes from the single plane study The feasibility of this approach has been established for the left ventricle almost a decade ago[4-8]

The attempts to measure angiographically the right ventricular volume parameters are relatively new Virtually all of them are of the biplane variety[9-15] The purpose of this report is to propose a technique which allows a single plane right ventricular cineangiography to be used for the derivation of right ventricular volume indices that could previously be determined only from the biplane analysis

Materials and methods

In our previous report human right ventricular (RV) casts were used to develop the mathematical model for RV volume calculations from the biplane cineangiograms After correction with a regression equation this mathematical model assumed the following expression

$$V_{RV} = 0.6 \; \frac{A_{RAO} \; A_{LAO}}{l_{RAO}} + 3.9 \qquad (1)$$

where V_{RV} = volume of right ventricle A_{RAO} and A_{LAO} = areas of the RV silhouette in 30 degree right anterior oblique (RAO) and 60 degree left anterior oblique (LAO) projections and l_{RAO} = longitudinal axis obtained by dividing the projected RAO image with a connecting line between the bisected pulmonic valve and the bisected base

Expression (1) can be reduced into an equation for the single plane volume calculations if the area in the LAO projection can be expressed as a function of the area in the RAO projection Accordingly nine human right ventricular casts were filmed in the 30 degree RAO and 60 degree LAO views Films of the casts were then projected on a screen and their outlines traced A 1 by 1 cm grid (filmed at the midlevel of each ventricular cast) was used for calibration purposes RAO and LAO outlines for each ventricular cast were then planimetered and the long axis in the RAO projection was determined

The A_{LAO}/A_{RAO} fraction was subsequently calculated for each individual cast The following relationship was established between the A_{RAO} and A_{LAO}

$$A_{LAO} = 0.668 \; (\pm 0.137) \; A_{RAO} \qquad (2)$$

This expression was then used to transform the biplane formula (1) into the equation for single plane RV volume determination

$$V_{RV} = 0.4 \; \frac{(A_{RAO})^2}{l_{RAO}} + 3.9 \qquad (3)$$

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Measurements of right ventricular volumes in man from single plane cineangiograms *

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Biplane and single plane volumes were then calculated from the two respective equations, and correlation coefficient (r) and regression equation were determined

Ten patients with the suspected coronary artery disease but with normal coronaries at the subsequent catheterization were selected for this study The mean patient age was 46 years All gave informed consent and underwent diagnostic catheterization including complete left and right heart hemodynamic evaluation, cardiac output determination, selective left ventriculography, and coronary arteriography In addition, biplane cine right ventriculograms in 30 degree RAO and 60 degree LAO projections were performed All patients were in normal sinus rhythm None had systemic hypertension, abnormal right heart hemodynamics, overt congestive heart failure, or significant valvular or congenital lesions

Biplane RV cineangiograms were performed and analyzed in the same manner as previously described[14] In addition single plane RV end diastolic volume index (EDVI) and end systolic volume index (ESVI) were also calculated and compared to the biplane values To determine if there was a significant change in the RV geometry during each cycle of its contraction A_{LAO}/A_{RAO} fractions were calculated for each patient in end diastole and in end systole and evaluated with the Student t test

All measurements were performed in duplicate by two independent observers, the interobserver and intraobserver differences were negligible

Results

A very good correlation between the biplane and the single plane RV cast volumes was obtained The biplane volumes ranged from 38 ml to 150 ml and single plane from 31 ml to 151 ml The correlation coefficient (r) for these two sets of values was 0 93

A plot of biplane volumes against the single plane volumes is presented in Fig 1 The regression equation calculated from this plot

$$y = 0.883x + 7.713 \qquad (4)$$

was used in an attempt to obtain an even better fit for the single plane RV volume expression (expression 3) The improvement was negligible, however, and the single plane formula (formula 3) was used in patient studies without any further modifications

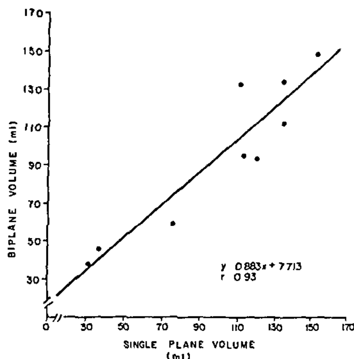


Fig 1 Biplane versus single plane right ventricular cast volumes

Table I Biplane vs single plane right ventricular volumes (± 1 S D) for ten normal patients (S E E in parentheses)

Method	*EDVI (ml/M²)*	*ESVI (ml/M²)*
Biplane	74 ± 16 (5)	26 ± 6 (2)
Single plane	69 ± 13 (4)	22 ± 5 (2)

Abbreviations EDVI = end diastolic volume index ESVI = end systolic volume index S D = standard deviation S E E = standard error of estimate

The results for the ten patients who had RV cineangiograms are presented in Table I The mean biplane and single plane values for EDVI and ESVI are almost identical The biplane volumes are slightly higher than their single plane counterparts but this difference is statistically not significant There was a small change in the A_{LAO}/A_{RAO} fraction from end systole to end diastole (0 101) This difference was again statistically not significant, indicating that a major change in the RV geometry does not occur during its contraction

Discussion

The studies investigating the RV performance have lagged considerably behind the efforts to characterize the left ventricular function To an

extent this is probably due to the fact that the left ventricle was generally considered to be the more important chamber of the heart Another major reason for this difference in emphasis however could be attributed to the difficulties which were encountered when the RV analysis was attempted Specifically the initial attempts to assess the RV volumes required the use of biplane cineangiograms[4] and the subsequent analysis of these films with the quite accurate but very cumbersome Simpson s rule[11] Biplane facilities are still not widely available neither are the computers which are almost mandatory if Simpson s method of analysis is to be efficiently performed Right ventricular volume analyses were therefore performed relatively rarely and then only in selected laboratories[9] [2] [3] even though that they yielded a great deal of very useful information especially in patients with congenital heart disease[8] [9]

More recently it became apparent that the much simpler area-length method[2] of the RV volume analysis is not only feasible but equally as accurate as the Simpson s rule if the mathematical model that is to represent the RV chamber is reasonably well chosen[9] [3] [5] Unfortunately all of these approaches still require the use of biplane RV cineangiograms

The present study was designed to evaluate the feasibility of deriving accurate RV volumes from a single plane angiogram by an area-length method and therefore make RV volume and ejection fraction analyses a simple procedure which can be routinely accomplished in virtually all cardiac catheterization laboratories whenever such information is desired for investigative or clinical purposes Right anterior oblique projection was selected because it orients the interventricular septum parallel to the film[2] and therefore yields the greatest expanse of the RV area An assumption was made that the A_{LAO} will remain relatively constant in relationship to the A_R and the subsequent A_{LAO}/A_{RAO} ratio was used to modify the biplane equation (equation 1) for the single plane use The validity of this approach was confirmed when the biplane and single plane volume calculations from the RV casts yielded almost identical values with a good correlation coefficient (0 93)

When tested on ten patients with a normal cardiac status single plane volumes deviated little from their biplane counterparts (Table I) To be certain that the single plane equation accurately represented RV images *in end systole and* in end diastole A_{LAO}/A_{RAO} ratios were calculated for each patient at these two end points Only a minimal deviation between the two respective ratios was observed This new approach to the RV volume analysis therefore yields not only very accurate RV cast data but also provides comparable values to biplane analysis when tested in patients It therefore represents a reasonable substitute for the biplane approach and can be readily used in the vast majority of the cardiac catheterization laboratories which lack the biplane cineangiographic facilities

Summary

An area-length expression for RV volume determination from single plane cineangiograms has been developed and verified against the biplane volumes with the aid of the RV human casts A close correlation was found to exist between the two methods (r = 0 93)

Ten patients with normal hearts were subsequently studied Biplane and single plane RV cineangiographic analyses yielded virtually identical results The single plane expression was equally valid in the end systolic and the end diastolic volume analysis

The author wishes to thank Ms S M *Savoy for her* extensive help in the analysis of the presented data

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Double outlet left ventricle associated with situs inversus and atrioventricular concordance

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Increasing knowledge of the precise morphology of rare congenital cardiac anomalies tends to facilitate their in vivo diagnosis and surgical correction The ventriculo arterial connection described as double outlet left ventricle (DOLV) was originally considered to be an embryological impossibility[1] [2] However its existence was proved by the anatomical and clinical presentation of Paul and colleagues Prior to that surgical correction of a heart in which both arteries arose from the morphological left ventricle had been reported by Sakakibara and associates Since then several additional cases have been recognized[3] but to the best of our knowledge all cases encountered to date have been from individuals having situs solitus The purpose of the present report is to describe an example of double outlet left ventricle from a patient with situs inversus

Case report

The patient a ten year old girl had been cyanosed from birth She was investigated elsewhere at the age of four years when the diagnosis of transposition of the great arteries with situs inversus, atrioventricular concordance ventricular septal defect pulmonary stenosis and dextrocardia was made At the age of six years a left subclavian to pulmonary artery (Blalock Taussig) shunt was performed She was referred to the Hospital for Sick Children for total correction of the anomalies

On examination the girl was severely cyanosed and exhibited gross clubbing of the fingers and toes Her height and weight were below the 10th percentile The cardiac impulse was right sided and a systolic thrill was palpable over the right parasternal region Auscultation revealed a normal first heart sound a single second sound a Grade 4/6 systolic murmur at the right third intercostal space and a continuous murmur beneath the left clavicle The latter was interpreted to indicate continuing function of the Blalock Taussig shunt The electrocardiogram showed sinus rhythm with a pattern typical of mirror image dextrocardia and systemic ventricular hypertrophy Chest x ray demonstrated moderate cardiomegaly with the heart situated in the right chest and oligemic lung fields. The stomach was right sided with a left sided liver The hemoglobin was 19 9 Gm per cent and the hematocrit was 57 per cent

Cardiac catheterization was performed and the hemodynamic data are given in Table I Cineangiocardiography was performed in both ventricles The morphological right ventricle was anterior and left sided and was entered from the systemic venous atrium also situated on the left The aortic valve was supported by a complete muscular conus (Figs. 1A and 2A) The pulmonary artery was also opacified by the right ventricular injection The left atrium was entered through an atrial septal defect and was right-sided The catheter was advanced through a second atrioventricular valve and another injection was made into the right sided ventricular chamber (Figs 1B and 2B) This chamber had the characteristics of a morphological *left ventricle* and was posterior and right sided The films were interpreted as exhibiting transposition of the great arteries (pulmonary artery from morphological LV aorta from morphological RV) (Figs 1 and 2) The hemodynamic data had indicated severe pulmonary stenosis and the angiograms revealed that this stenosis was at both valvar and subvalvar levels (Fig 2B)

At operation the heart was exposed through a midline sternotomy The left Blalock Taussig shunt was ligated and the patient was connected to the heart lung machine Following inspection of the right ventricle after institution of cardiopulmonary bypass, it was established that the ventriculo-arterial connection of double-outlet left ventricle was present the aorta being completely above the morphological right ventricle was through a large *anterior* ventricular septal defect in sub-aortic position A Rastelli type repair was performed. VSD was closed with a Teflon patch from the right ventricle. The main pulmonary artery was then transected and the ventricular end was oversewn A Dacron tube incorporating a homograft aortic valve was placed between the

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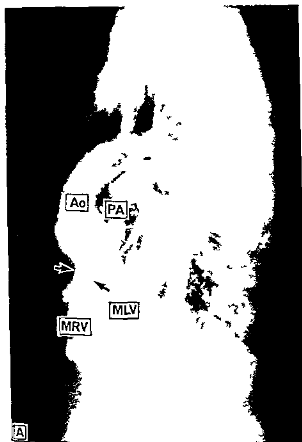


Fig 2A Lateral projection of the same injection illustrated in *Fig 1A* The dye can be seen passing from the morphological right ventricle *(MRV)* into the left ventricle *(MLV)* through a ventricular septal defect *(between arrows)* The posteriorly placed pulmonary artery *(PA)* and more than half the aorta *(Ao)* are above the left ventricle

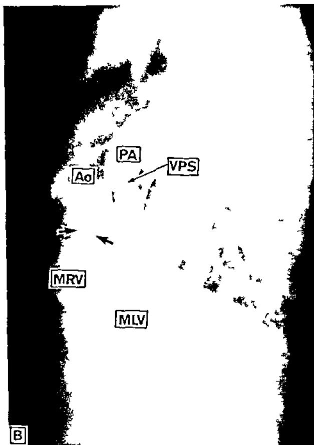


Fig 2B Lateral projection of the same injection illustrated in *Fig 1B* The morphological left ventricle *(MLV)* is posterior and gives rise to both aorta *(Ao)* and pulmonary artery *(PA)* The pulmonary valve is thickened and shows dome shaped stenosis *(VPS)* Note the sub aortic position of the ventricular septal defect *(between arrows)* and that the anterior morphological right ventricle *(MRV)* fills through the defect

The pulmonary outflow tract was grossly constricted at its ventricular origin by a fibrous ring composed of the conus septum anteriorly and the area of pulmonary-mitral fibrous continuity posteriorly (Fig. 3C) There was additional dome shaped stenosis of the pulmonary valve above this diaphragm

The pathological diagnosis was

1 Inversus-concordant-double outlet left ventricle
2 l malposition of the aorta
3 Sub-aortic ventricular septal defect
4 Sub valvar and valvar pulmonary stenosis.
5 Hypoplasia of morphological right ventricle and tricuspid valve
6 Patent foramen ovale

Discussion

As the ventriculo arterial connection of double outlet left ventricle becomes recognized with increasing frequency it is evident that it can exist with considerable variation in both great arterial interrelationships and conal morphologies [3,7] Our present case indicates that it can exist in patients with situs inversus as well as in individuals with situs solitus and one of us has recently seen an example of this ventriculo arterial connection with atrioventricular discordance [2] These findings exemplify the need for a segmental approach to nomenclature such as promoted by Van Praagh[8] and Kirklin [9] together with the need for describing arterial interrelationships and ventricular septal defect position as in the commoner but comparable malformation of double outlet right ventricle [9] However it should be appreciated that double outlet left ventricle is a rare condition

In our case as with several of the other diagnosed cases of double outlet left ventricle (DOLV) the ventriculo arterial connection had previously been considered to represent a different connection in this instance transposition

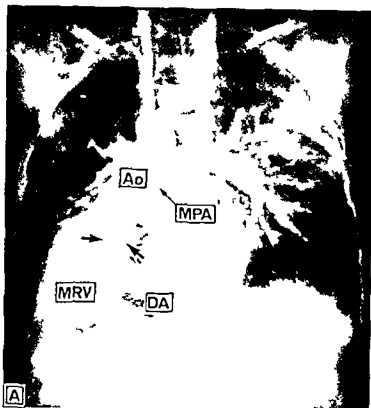


Fig 1A Angiocardiogram in the systemic venous ventricle anteroposterior projection The catheter has been advanced *through the left sided inferior vena cava through the left* sided systemic venous atrium and into the ventricle which is anterior and has the characteristics of a morphological right ventricle *(MRV)* Note the presence of dextrocardia and the right sided descending aorta *(DA)* Both arteries are opacified by this injection filling via a ventricular septal defect *(between arrows)* The aorta *(Ao)* is almost directly anterior to the pulmonary artery *(MPA)* at valve level

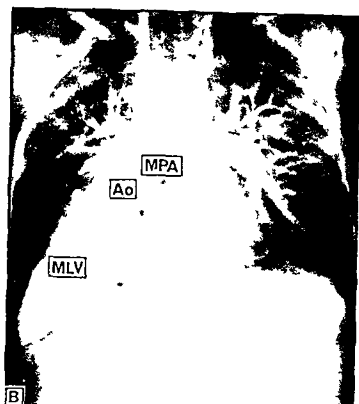


Fig 1B Angiocardiogram in the pulmonary venous ventricle anteroposterior projection The catheter has been advanced from the left sided systemic venous atrium through a patent foramen ovale and through the pulmonary venous atrium into a chamber with the morphological characteristics of the left ventricle *(MLV)* The ventricle is right sided and gives rise directly to both great arteries (*Ao* MPA)

distal main pulmonary artery and the anterior wall of the morphological *right ventricle Patent foramen ovale was* closed On conclusion of bypass the systemic venous atrial pressure remained excessively high and after a stormy postoperative period the girl died eight days later in low cardiac output and renal failure

Necropsy findings Complete viscero atrial situs inversus was present and abnormal findings were confined to the heart The *morphological right atrium was left sided and received* the superior and inferior caval veins and a coronary sinus (Fig 3A) The patent foramen ovale had been closed by direct suture The right atrium opened through a small tricuspid valve (Fig 4) into a hypoplastic sinus portion of the morphological right ventricle The papillary muscle pattern was typical of a normal tricuspid valve and a well formed *trabecula septomarginalis* (septal band) was present on the septal surface of the ventricle The only exit from this ventricle was through an anterior ventricular septal defect which was firmly closed by a Dacron patch (Fig 3C) The roof of the defect was the left margin of the conoventricular flange which separated the aortic valve from the tricuspid valve A conduit was present between the anterior wall of the right ventricle and the pulmonary artery All suture lines were intact The morphological left atrium was right sided and received four pulmonary veins (Fig 3B) It communicated through a mitral valve with the morphological left ventricle

Table I Cardiac catheterization data (July 7, 1971) on patient A T (date of birth Mar 1 1964)

Site	*Oxygen saturation (%)*	*Pressure (mm Hg)*
Superior vena cava	47	
Inferior vena cava	45	
Right atrium	60	$\bar{8}$
Right ventricle	65	95/0/14
Pulmonary artery	71	22/16 $(\overline{18})$
Pulmonary veins	94	
Left atrium	76	$\bar{8}$
Left ventricle	77	100/0/12
Aorta	74	100/60 $(\overline{75})$

Right and left refers here to the anatomic chambers not to the position within the thorax

Anteriorly both great *arteries arose from the morphological* left ventricle The aortic valve was anterior to the pulmonary valve and slightly to its left It was separated from the pulmonary valve by the conus septum and its superior left border was the conoventricular flange (Fig 3C) As judged from the specimen the aorta arose in its entirety from the morphological left ventricle

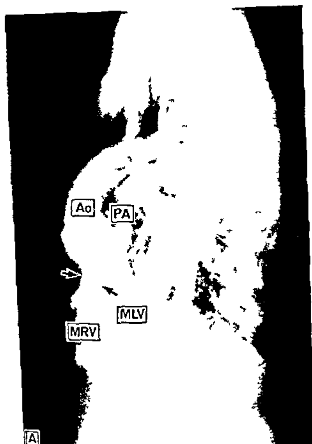


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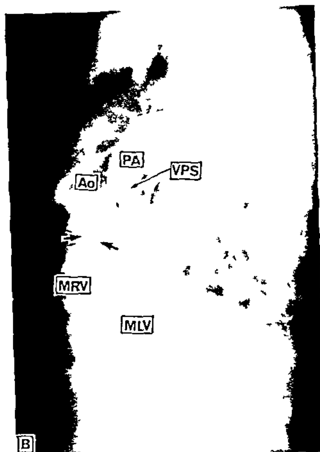


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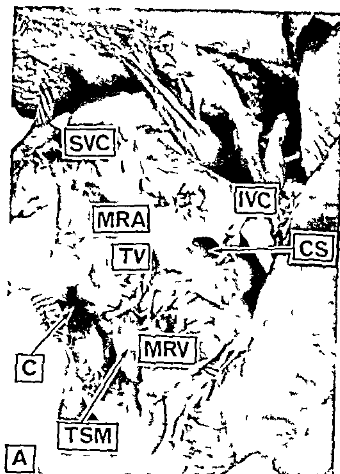


Fig 3A Photograph of the systemic venous chambers which are left sided The morphological right atrium *(MRA)* receives the superior and inferior caval veins *(SVC IVC)* and the coronary sinus *(CS)* It communicates through a morphological tricuspid valve *(TV)* with the morphological right ventricle *(MRV)* Note the *trabecula septomarginalis* on the septal surface *(TSM)* The septal defect has been closed with a Dacron patch *(P)* Note the ventricular insertion of the valved conduit *(C)* placed to bypass the pulmonary obstruction

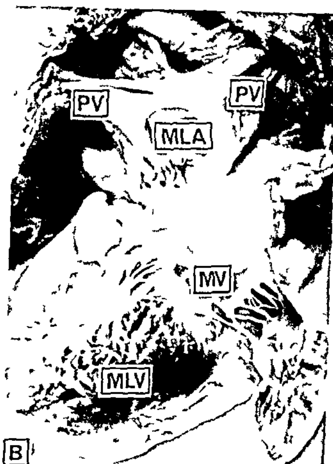


Fig 3B Photograph of the pulmonary venous chambers which are right sided The morphological left atrium *(MLA)* receives the pulmonary veins *(PV)* and communicates with the morphological left ventricle *(MLV)* via a mitral valve *(MV)*

When we reviewed the angiocardiograms after the operation, we realized that what had been interpreted as a ventricular septal defect was in fact the subaortic conus and that on some frames over 50 per cent of the aortic valve was above the left ventricle Hence employing the criterion of Kirklin and associates [9] it was an example of DOLV However making the diagnosis of transposition was not a serious error because the correct diagnosis of DOLV at surgery is not difficult and the surgical approach is similar *Correction of DOLV is actually easier than that of* transposition with ventricular septal defect (VSD) and pulmonary stenosis because one can simply close the VSD there being no need to create an intracardiac funnel from the left ventricle to the aorta Placement of a valved conduit between the right ventricle and the pulmonary artery is then identical

The surgical repair in our case was carried out in a similar fashion to the four cases described by Pacifico and colleagues and the case described by Conti and associates [10] Thus the ventricular septal defect was closed together with the main pulmonary artery and a valved conduit was placed between the morphological right ventricle *and the transected main pulmonary artery* The fatal outcome in our case was we believe a consequence of the severe tricuspid orificial hypo plasia a feature not suspected either pre or intraoperatively However by the very nature of the condition in that the right ventricle possesses no infundibulum right ventricular hypoplasia and possible tricuspid hypoplasia should always be suspected It may be preferable in these *patients therefore to consider a Fontan type* operation,[11] i e placing a conduit between the right atrium and the pulmonary artery and oc cluding the hypoplastic tricuspid orifice

Summary

A case is described in which the ventriculo arterial connection of double outlet left ventricle was associated with situs inversus and atrioven



Fig 3C Photograph of the anterior part of the morphological left ventricle (MLV) which is right sided Both aorta (Ao) and pulmonary artery (PA) arose directly from this ventricle Note the sub aortic position of the ventricular septal defect (VSD) which is closed by a Dacron patch To the left the aortic valve is separated from the tricuspid valve in the roof of the defect by the conoventricular flange (CVF) Posteriorly it is separated from the pulmonary valve by the conus septum (CS) A fibrous constriction ring is formed round the pulmonary outflow tract between the conus septum and the area of pulmonary mitral valvar continuity (arrowed)

tricular concordance The case additionally exhibited l malposition of the aorta a subaortic ventricular septal defect and valvar and sub valvar pulmonary stenosis Originally diagnosed as transposition of the great arteries a Rastelli type correction was attempted This was not successful owing to hypoplasia of the morphological tricuspid valve orifice

We are indebted to Dr Jane Somerville for permission to refer to an as yet unpublished case We thank the photographic departments of the Ludwig Institute for Cancer Research and the Hospital for Sick Children London Mrs. S Y Ho provided invaluable technical assistance and Miss M Huntington assisted in the preparation of the manuscript

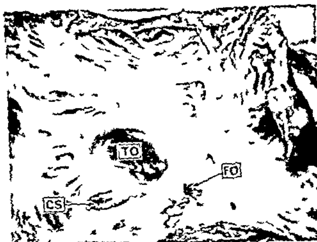


Fig 4 Photograph of the opened and left-sided right atrium showing the hypoplastic tricuspid valve orifice (TO) Note the stitches closing the foramen ovale (FO) and the coronary sinus (CS)

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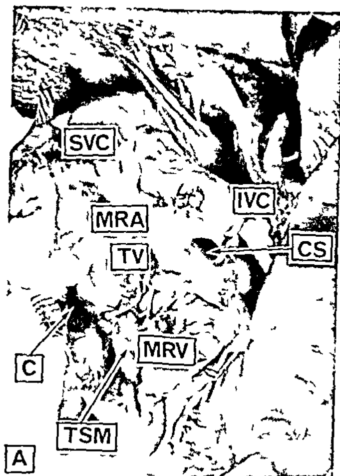


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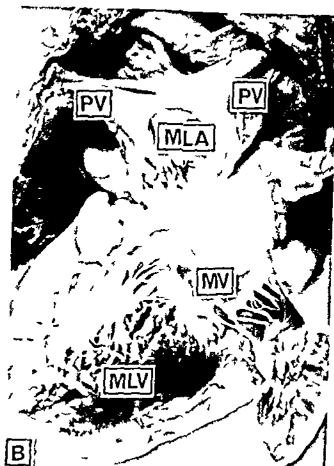


Fig 3B Photograph of the pulmonary venous chambers which are right sided The morphological left atrium (MLA) receives the pulmonary veins (PV) and communicates with the morphological left ventricle (MLV) via a mitral valve (MV)

When we reviewed the angiocardiograms after the operation, we realized that what had been interpreted as a ventricular septal defect was in fact the subaortic conus and that on some frames over 50 per cent of the aortic valve was above the left ventricle Hence employing the criterion of Kirklin and associates[9] it was an example of DOLV However making the diagnosis of transposition was not a serious error because the correct diagnosis of DOLV at surgery is not difficult and the surgical approach is similar Correction of DOLV is actually easier than that of transposition with ventricular septal defect (VSD) and pulmonary stenosis because one can simply close the VSD there being no need to create an intracardiac funnel from the left ventricle to the aorta Placement of a valved conduit between the right ventricle and the pulmonary artery is then identical

The surgical repair in our case was carried out in a similar fashion to the four cases described by Pacifico and colleagues[6] and the case described by Conti and associates[10] Thus the ventricular septal defect was closed together with the main pulmonary artery and a valved conduit was placed between the morphological right ventricle and the transected main pulmonary artery The fatal outcome in our case was we believe a consequence of the severe tricuspid orificial hypoplasia a feature not suspected either pre or intraoperatively However by the very nature of the condition in that the right ventricle possesses no infundibulum right ventricular hypoplasia and possible tricuspid hypoplasia should always be suspected It may be preferable in these patients therefore to consider a Fontan type operation[11] i e placing a conduit between the right atrium and the pulmonary artery and occluding the hypoplastic tricuspid orifice

Summary

A case is described in which the ventriculoarterial connection of double outlet left ventricle was associated with situs inversus and atrioven

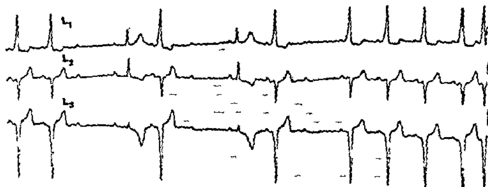


Fig 1 Lead 1 2 and 3 recorded simultanously with a paper speed of 25 mm/sec The first and second beat from the left are conducted over the accessory pathway After the third P wave there is a total atrioventricular conduction block The pause is terminated by a narrow escape beat

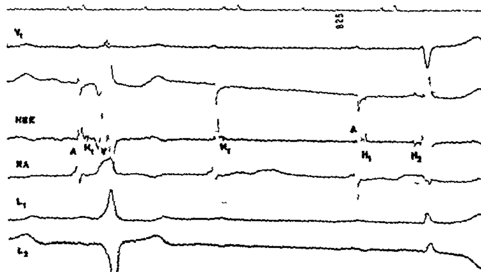


Fig 2 V = Lead V 1 *HBE* = His bundle recording (filtered below 40 and above 500 Hz) *RA* = high right atrial lead L = Lead 1 L = Lead 2 The lead between V and HBE is the unfiltered HBE Paper speed 100 mm/sec Every A spike is followed by an H spike (H) and every V spike is preceded by an H spike (H) The first beat conducts over the accessory pathway and only H can be identified The H V interval is 50 msec

of pre excitation configuration of the QRS complex because conduction in the A V nodal His pathway would be too fast and would result in normal QRS complexes During total A V block distal to the origin of the accessory bypass tract however a relatively long conduction in the accessory pathway can still result in pre excitation of the ventricle The conduction time of the bypass tract depends on its geometry There fore a thin long or diseased bypass tract can be assumed in our case The refractory period of the bypass could not be determined since a Mobitz Type 2 block occurred immediately during atrial pacing The latter in conjunction with the imme diate block after application of drugs which are known to increase the refractory period of the pathway are indicative of a very long refrac tory period of the bypass tract

There are only a few similar cases described in the literature Masini and Milazotto described a case with intermittent Wolff Parkinson White syndrome right bundle branch block left poste rior fascicular block and total A V block The idioventricular rhythm showed wide QRS com plexes thus making the assumption of a distal block possible No His bundle recording was performed in this case Masini and Milazotto interpreted their findings with a bypass tract

Pre-excitation of the ventricle associated with total intra His bundle block

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Better understanding of the conduction proper ties of the atrioventricular conduction system has been achieved by programmed stimulation com bined with His bundle recordings [1-3] In pre excita tion syndrome the conduction properties of the pathways are different and several combinations of disturbances can occur during atrial pacing [4, 5] We would like to present a combination of total intra His block and intermittent pre excitation syndrome

Case report

A 70 year old woman has been suffering for four years from bouts of dizziness and episodes of tachycardia otherwise she presented in good general condition Her electrocardiogram showed pre excitation of the ventricle with periods of no conduction from the atrium to the ventricle (Fig 1) After a pause escape beats with a normal width of QRS complexes occurred

Electrophysiological studies The His bundle recording in the above described ECG showed an H spike following every A spike and an H spike preceding every V spike of the narrow escape beats thus giving the typical appearance of an intra His block (Fig 2) [*] The conducted beats with a pre excitation configuration of the QRS complex showed a relatively long P delta interval of 130 msec with an A H interval of 60 msec and a P(high right atrium) A interval of 20 msec During atrial pacing a 2 1 block in the accessory pathway occurred at a cycle length of 600 and 500 msec a 3 1 block occurred with a cycle length of 430 msec and an intermittent total block with narrow escape beats preceded by a His spike with a cycle length of 375 msec (Fig 3) The A H interval of the paced P waves increased to 130 msec and the H V interval of the conducted beats to 70 msec at a cycle length of 375 msec (Table I)

It is important to note that at increasing rates the conducted beats showed an increasing P delta interval The conducted beats had only one His bundle spike During pacing from the right ventricle there was no retrograde conduction to the atrium at all

A demand pacemaker (Medtronic 5951) was implanted and it was turned off during constant accessory pathway conduc tion by transcutaneous stimulation of the unit by an external pacemaker (Cambridge MP 16) 35 mg Ajmaline administered intravenously resulted in a total block in the accessory pathway after one minute The escape beats of the idioventric ular rhythm which occurred after a pause had a narrow QRS complex (Fig 4) This effect lasted for 7 minutes until conduction through the accessory pathway resumed The same result could be achieved with 50 mg Propafenon intra venously [26]

Discussion

These electrophysiologic findings can be inter preted as follows There is a complete intra His bundle block proved by a constant appearance of an H_1 spike after every A spike and an H spike preceding every escape beat during block in the accessory pathway During the conduction to the ventricle there is only one H spike with a normal A H_1 time It is assumed that during conduction only the accessory pathway is used The increas ing P delta interval primarily caused by an A H_1 prolongation during increasing pacing rates must be explained by the origin of the accessory pathway in or after the A V node but before the site of block (Fig 5) These fasciculoventricular or nodoventricular fibers [9, 11] described by Mahaim and Winston [12] can be theoretically recognized by a short H-V interval In our case it is 50 msec which is normal in our laboratory (35 to 55 msec) and increases to 70 msec during rapid atrial pacing This may be explained by a long conduc tion time of the impulse in the bypass tract originating before the site of block During normal A V conduction this would result in loss

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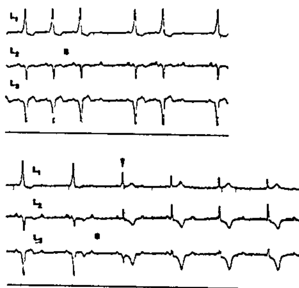


Fig 4 Discontinuous strip of Leads 1 2 and 3 at a paper speed of 25 mm/sec S = pacemaker spike of an external pacemaker (Cambridge MP 16) (see text) After administration of Ajmalin first a 2 1 block in the accessory pathway and then a total A V block with narrow escape beats occurs One beat *(arrow)* is a fusion beat between a conducted beat and an escape beat

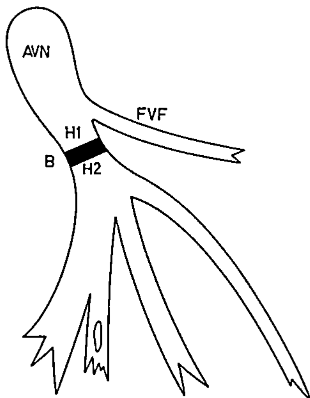


Fig 5 Scheme of the A V conduction system with the assumed site of block and origin of the accessory pathway *AVN* = A V node *B* = site of block in the His bundle H = recording site of H H = recording site of H and origin of the escape beats *FVF* = fasciculoventricular fibers or nodoventricular fibers

with Wolff Parkinson White syndrome who did not show ventriculoatrial conduction over the accessory pathway

Summary

A case with total intra His bundle block and intermittent pre excitation syndrome is presented During A V conduction there was a P delta interval of 130 msec with a P A interval of 20 msec an A H interval of 60 msec and an H V interval of 50 msec During rapid atrial pacing the P delta interval increased primarily due to an A H prolongation and a Mobitz type 2 block and total A V block occurred at increasing rates showing H following every A spike The escape beats showed a normal width of the QRS complexes with preceding H_2 spikes After administration of Ajmaline the bypass tract was blocked and constant total A V block occurred

It was concluded that there was a constant total intra His bundle block and a nodoventricular or fasciculoventricular bypass tract with prolonged conduction to the ventricle This bypass tract blocked sometimes spontaneously and could also be blocked by rapid atrial pacing and administration of drugs The close anatomic proximity of the His bundle and Mahaim fibers is responsible for the simultaneous block resulting in total atrioventricular block

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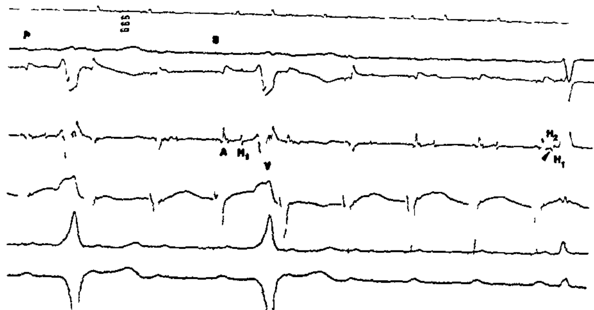


Fig 3 Abbreviations and order of leads as in *Fig 2* *P* = P wave *S* = pacemaker spike Paper speed 100 mm /sec S S interval 375 msec P(=high right atrium)delta interval 230 msec Every A spike is followed by an H spike The A H_1 interval is 130 msec Total block occurs distal to the His bundle and the pause is terminated by a narrow escape beat (100 msec) which is preceded by an H_2 spike *(arrow)* In this case H comes before H because of the proximity of the adjacent A spike which conducts into the His bundle

Table I Conduction times during spontaneous rate and rapid atrial pacing*

Spontaneous rate						*Rapid atrial pacing*					
PP interval (msec)	*PA interval (msec)*	*P delta interval (msec)*	*AH_1 interval (msec)*	*H V interval (msec)*	*Block*	*SS† interval (msec)*	*SA interval (msec)*	*S delta interval (msec)*	*AH interval (msec)*	*H V interval (msec)*	*Block*
850	20	130	60	50	OEB†	600	20	150	80	50	2 1
						500	20	170	100	50	2 1
						430	20	190	110	60	3 1
						375	20	220	130	70	4 1 +OEB

At increasing rates the P delta interval increases due to a marked prolongation of the AH interval At higher rates the H V interval increases slightly and a block showing H following every A spike occurs The increased H V interval is due to prolonged conduction in the accessory pathway
†Abbreviations SS = interval of the pacemaker spikes OEB = occasional escape beats with narrow QRS and preceding H

running close to the anterior fascicle of the left bundle so that sometimes both can be blocked simultaneously [15] A very similar case was reported by Massumi [16] In his case a trifascicular block occurred two years after bifascicular block was observed He demonstrated that a pre excitation pathway blocked and conducted together with the normal pathways For this reason he suggested that the anomalous bundle and the normal pathway *travelled together* [16]

In our case there is evidence of an intra His bundle block and the existence of nodoventricular or fasciculoventricular fibers The anatomic proximity of these two structures is obvious and thus the possibility that both can be involved in the same pathologic process seems quite realistic Lev and colleagues[17] reported one case in which our assumption was proved by histologic investigation of the heart Coumel[18] described four cases of pre excitation syndrome and total A V block Only one was of degenerative etiology In contrast to our case, retrograde conduction was more consistent than antegrade conduction this is not surprising since the experimental studies of De la Fuente and associates [12] Our case belongs obviously to the group without ventriculoatrial conduction at least at the time of study Wellens and Durrer[19] described eight out of 36 patients

Prevention of arterial thromboembolism with acetylsalicylic acid

A CONTROLLED CLINICAL STUDY IN PATIENTS WITH AORTIC BALL VALVES

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Erik Myhre M D
Ole Storstein M D
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Drugs that modify platelet function may be of value in the prevention of arterial thromboembolism Acetylsalicylic acid (ASA) has been found to inhibit the platelet release reaction induced by collagen adenosine diphosphate (ADP) or epinephrine in vitro [2] Secondary platelet aggregation caused by epinephrine or ADP is associated with release of endogenous ADP [3] This response disappears after intake of ASA [5] Ingestion of ASA inhibits release of ADP and the subsequent aggregation induced by connective tissue particles [6] Other anti inflammatory drugs also inhibit the release reaction [4,7] Dipyridamole is a rather weak inhibitor of aggregation in vitro[1] and has little effect on platelet aggregation after in vivo administration [2,8,9]

Patients with prosthetic heart ball valves run a considerable risk of developing arterial emboli [11] Although well performed anticoagulant treatment has been found to offer some protection [2] the frequency of embolic episodes is high despite anticoagulant therapy [1] Even if several experimental and clinical studies have documented an antithrombotic effect of drugs that inhibit platelet aggregation and especially of ASA [2,16] the role of antiaggregating drugs in the prevention of arterial thrombosis has not been definitely settled Sullivan and associates[17] investigated the effects of dipyridamole on thromboembolism in ball valve patients and found that the frequency of embolic episodes was significantly lower in patients receiving the drug than in the placebo group All patients were given anticoagulant therapy

The effects of ASA and dipyridamole on platelet functions in patients with prosthetic aortic valves have been previously evaluated [18] ASA in a daily dose of 2 Gm considerably prolonged the bleeding time reduced platelet aggregation induced by collagen particles and inhibited the second phase of aggregation initiated by epinephrine in citrated platelet rich plasma (PRP) while the platelet survival rate was unchanged Dipyridamole 375 mg daily did not affect any of the functions

We wanted to study the antithrombotic effects of a drug affecting platelet function and chose ASA because of its ability to reduce the release dependent platelet aggregation after ingestion Patients with aortic ball valve prostheses were suitable because of their strong tendency toward arterial thromboembolism

Material and methods

Starting in June 1972 all patients with a single Starr Edwards aortic ball valve were asked to come for examination The implantations had been performed in this hospital from 1967 to 1970 the patients came from all parts of the country [illegible] valves of Starr Edwards type 1200

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with silicone rubber ball and metal cage, and type 2300 with hollow Stellite ball and cloth covered cage,[19] were implanted in 253 persons, patients with double or triple valves were excluded from the study The number of deaths during operation and the first postoperative month was 37, 41 late deaths occurred Of the 175 surviving patients, 169 were examined

A careful clinical examination was performed to evaluate the function of the myocardium and heart valves and to reveal thromboembolic episodes bleeding anemia, and other complications and diseases The degree of intravascular hemolysis platelet function, coagulation, and fibrinolysis were studied, and electroencephalography (EEG) was done before and after the trial The results of these investigations will be published separately

After this examination 21 patients were excluded from participation in the study The main reasons for exclusion were age higher than 70 years a history of gastrointestinal or other bleeding and planned heart operations The remaining 148 patients were all willing to participate They received either 1 Gm of microencapsulated ASA daily, divided in two doses or placebo according to a randomized list Tablets containing 0 5 Gm of ASA or placebo were prepared by Bayer AG and designated Colfarit A and B Which tablets contained the active drug remained a secret with the manufacturer until the study was completed, and the author who conducted the investigation and examined the patients did not know what preparation was given to them Thus the study was, in effect double blind No Colfarit preparations are commercially available in Norway and the patients were strictly forbidden to take any other drugs containing ASA or other anti inflammatory agents A list containing all registered forbidden preparations specified was given to each of them All patients received anticoagulant therapy the intensity of which was controlled by Thrombotest (TT) ° aiming at a level of 10 per cent of normal activity In 60 of the patients the treatment was directed by us in the remaining patients by local hospitals The doctors of all patients were informed about the study and asked to report changes of any kind

We decided that ASA or placebo should be discontinued after all acute complications except those related to thromboembolism and cardiocirculatory performance, and the doctors were instructed accordingly This was done in order to avoid possible ill effects of the combined treatment with ASA and anticoagulants

After approximately one year, all patients except those who lived in the northernmost part of Norway were re examined in this hospital the remainder were controlled by their local physicians who reported their findings on a special questionnaire In addition, a request was sent to each patient's doctor, asking for a report of any thromboembolic episodes bleeding, and other observations At this time a clinical examination was done and x ray, ECG, and several blood tests were repeated The plasma levels of salicylate were determined in order to estimate how well the patients followed their drug instructions and the results were not revealed until the study was closed

Since a number of gastrointestinal bleeding episodes had occurred at low TT values, the doctors were again advised to keep the levels strictly in the range of 10 to 12 per cent, and especially to avoid lower values

The final examination was performed after 2 years Of the 148 patients included in the study, 139 were still alive and 132 reported for examination As before, the remaining patients were controlled by their physicians and questionnaires were sent to the doctors of all patients in order to obtain complete information

A third group of patients was observed in addition to those on ASA or placebo This group consisted of patients not given either of these preparations, one of whom had also died in the course of the study Patients whose medication had been discontinued for one reason or another were naturally included in this third group for the rest of the observation time

In addition to a clinical examination, the ECG, EEG, x ray, and most blood tests were repeated At this time, three stool specimens from each patient were examined for occult blood by the benzidine method

The diagnosis of thromboembolic complications was based upon the following criteria (1) acute onset with full development of symptoms in the course of 20 minutes (2) disturbance of neurological function in cerebral embolism or functional disturbance due to arrested blood flow in other regions, (3) observation of the symptoms by other persons than the patient, (4) duration of

Table I Random distribution of patients in groups receiving either ASA or placebo Type of Starr Edwards aortic ball valve number of arterial thromboembolic episodes from the second month postoperatively until the start of the study and number of patients with continuous arrhythmia and concomitant mitral disease in each group

	ASA	*Placebo*
Patients		
No of patients	75	73
No of men	58	53
No of women	17	20
Mean a e at operation (yr)	*50 1*	*51 4*
Mean time since operation (mo)	42 4	41 1
Type of Starr Edwards valve		
Series 1[illegible]00 no of patients	23	21
Series 2300 no of patients	52	52
Previous arterial thromboembolic complications		
No of thromboembolic episodes	15	11
No of patients with episodes	12	10
Continuous arythmia and mitral disease		
Arrhythmia no of patients	1[illegible]	8
Mitral disease no of patients	19	17

symptoms for more than half an hour Myocardial infarction was diagnosed when there was a history of acute precordial pain ECG signs and rise of temperature leukocye counts or transaminases Alternatively arterial thromboembolism could be diagnosed at autopsy or at operation

Results

In Table I a comparison is made between the groups of patients receiving ASA and placebo The two groups are quite similar with regard to number of patients sex distribution age time since operation and valve type The number of arterial thromboembolic episodes from the second postoperative month until the study started was slightly higher in the ASA group as was the number of patients with continuous arrhythmia or concomitant mitral disease The differences are not statistically significant and the groups are fairly comparable

A total of 12 arterial thromboembolic complications were diagnosed in 10 of the patients in the placebo group and three of them died (Table II) A 59 year old woman (S U) who lived alone was talking to a friend on the telephone when she complained of sudden and strong headache and

Table II Arterial thromboembolic complications in patients receiving anticoagulants and placebo Type of complication and TT values at or immediately before thromboembolic episodes

Patient	*Sex age*	*Thromboembolic complication*	*Death*	*TT value (%)*
S U	F 59	Embolia cerebri	+	15
A. P	M 53	Embolia cerebri	+	9
E. E.	M 37	Embolia cerebri	+	10
O B	M 62	Embolia cerebri		9
		Embolia cerebri		12
M B	M 65	Embolia cerebri		12
B H	M 43	Embolia cerebri		10
S S	M 66	Embolia cerebri		2[illegible]
		Embolia a brachialis		8
T A.	M 60	Embolia a retinalis		12
A. R	M 6[illegible]	Embolia a retinalis		12
E B	M 6[illegible]	Infarctus cordis		11

said that she had to hang up the receiver The friend called back immediately but got no answer Arriving at the flat some minutes later she found the patient dead in a chair close to the telephone Unfortunately the doctor who was called was not aware of our study and an autopsy was not performed however the death was most probably caused by a cerebral embolus

Another patient (A P) one day complained of headache On the following day he gradually went into a deep coma and died 2 days later At autopsy a subdural hematoma containing 150 ml of blood was found and an embolus lodged in the middle cerebral artery There was no anatomical connection between bleeding and embolus and no history of trauma could be revealed Whether death was due to the hematoma or the embolus was difficult to assess but the neuropathologist thought it most likely that the bleeding had occurred first and was of the greatest significance

A 37 year old man (E E) who had been hospitalized once before because of a cerebral embolus developed a second serious embolic complication 13 weeks after inclusion in the study This resulted in permanent paresis and impairment of intellectual function He was deeply depressed because of the damage and committed suicide one year later At autopsy old bilateral cerebral infarcts were found

Two other cerebral emboli in the placebo group gave slight permanent sequelae mainly speech disturbances (patients O B and B H) Three of

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A third group of patients was observed in addition to those on ASA or placebo This group consisted of patients not given either of these preparations one of whom had also died in the course of the study Patients whose medication had been discontinued for one reason or another were naturally included in this third group for the rest of the observation time

In addition to a clinical examination the ECG, EEG x ray, and most blood tests were repeated At this time three stool specimens from each patient were examined for occult blood by the benzidine method

The diagnosis of thromboembolic complications was based upon the following criteria (1) acute onset with full development of symptoms in the course of 20 minutes (2) disturbance of neurological function in cerebral embolism or functional disturbance due to arrested blood flow in other regions (3) observation of the symptoms by other persons than the patient, (4) duration of

Table I Random distribution of patients in groups receiving either ASA or placebo. Type of Starr-Edwards aortic ball valve, number of arterial thromboembolic episodes from the second month postoperatively until the start of the study, and number of patients with continuous arrhythmia and concomitant mitral disease in each group

	ASA	*Placebo*
Patients		
No. of patients	75	73
No. of men	58	53
No. of women	17	20
Mean age at operation (yr.)	50.1	51.4
Mean time since operation (mo.)	42.4	41.1
Type of Starr-Edwards valve		
Series 1200, no. of patients	23	21
Series 2300, no. of patients	52	52
Previous arterial thromboembolic complications		
No. of thromboembolic episodes	15	11
No. of patients with episodes	12	10
Continuous arythmia and mitral disease		
Arrhythmia, no. of patients	12	8
Mitral disease, no. of patients	19	17

symptoms for more than half an hour. Myocardial infarction was diagnosed when there was a history of acute precordial pain, ECG signs, and rise of temperature, leukocye counts, or transaminases. Alternatively, arterial thromboembolism could be diagnosed at autopsy or at operation.

Results

In Table I a comparison is made between the groups of patients receiving ASA and placebo. The two groups are quite similar with regard to number of patients, sex distribution, age, time since operation, and valve type. The number of arterial thromboembolic episodes from the second postoperative month until the study started was slightly higher in the ASA group, as was the number of patients with continuous arrhythmia or concomitant mitral disease. The differences are not statistically significant and the groups are fairly comparable.

A total of 12 arterial thromboembolic complications were diagnosed in 10 of the patients in the placebo group and three of them died (Table II). A 59-year-old woman (S. U.) who lived alone was talking to a friend on the telephone when she complained of sudden and strong headache and said that she had to hang up the receiver. The friend called back immediately but got no answer. Arriving at the flat some minutes later she found the patient dead in a chair close to the telephone. Unfortunately, the doctor who was called was not aware of our study and an autopsy was not performed; however, the death was most probably caused by a cerebral embolus.

Another patient (A. P.) one day complained of headache. On the following day he gradually went into a deep coma and died 2 days later. At autopsy a subdural hematoma containing 150 ml of blood was found and an embolus lodged in the middle cerebral artery. There was no anatomical connection between bleeding and embolus and no history of trauma could be revealed. Whether death was due to the hematoma or the embolus was difficult to assess, but the neuropathologist thought it most likely that the bleeding had occurred first and was of the greatest significance.

A 37-year-old man (E. E.) who had been hospitalized once before because of a cerebral embolus developed a second serious embolic complication 13 weeks after inclusion in the study. This resulted in permanent paresis and impairment of intellectual function. He was deeply depressed because of the damage and committed suicide one year later. At autopsy old bilateral cerebral infarcts were found.

Two other cerebral emboli in the placebo group gave slight permanent sequelae, mainly speech disturbances (patients O. B. and B. H.). Three of

Table II Arterial thromboembolic complications in patients receiving anticoagulants and placebo. Type of complication and TT values at or immediately before thromboembolic episodes

Patient	Sex, *age*	Thromboembolic *complication*	*Death*	*TT value (%)*
S. U.	F 59	Embolia cerebri	+	15
A. P.	M 53	Embolia cerebri	+	9
E. E.	M 37	Embolia cerebri	+	10
O. B.	M 62	Embolia cerebri		9
		Embolia cerebri		12
M. B.	M 65	Embolia cerebri		12
B. H.	M 43	Embolia cerebri		10
S. S.	M 66	Embolia cerebri		22
		Embolia a. brachialis		8
T. A.	M 60	Embolia a. retinalis		12
A. R.	M 62	Embolia a. retinalis		12
E. B.	M 62	Infarctus cordis		11

Table III Arterial thromboembolic complications in patients receiving ASA and anticoagulants Duration of ASA administration and TT value

Patient	*Sex age*	*Thromboembolic complication*	*ASA (wk)*	*TT value (%)*
E L	F 50	Embolia cerebri	95	12
E S	M 36	Embolia a retinalis	48	8

the 10 patients with arterial thromboembolic complications in this group had suffered from cerebral emboli before the study started two of them (E E and S S) once and one (B H) twice before

Arterial embolism occurred only twice in patients receiving ASA (Table III) A 50 year old woman (E L) had symptoms typical of a cerebral embolus, with moderate residual speech difficulties and slight pareses In the other (E S) who had earlier had a cerebral embolic episode with transient symptoms a retinal embolus caused vision disturbance that lasted for only a few hours

The numbers of observation months in the individual patients were added for each group (Table IV) The incidence of arterial thromboembolic complications was calculated to be 9 32 episodes per 100 patients per year in the placebo group as compared to 1 76 in the patients taking ASA This difference is statistically significant ($p < 0.01$)

The incidence of late arterial thromboembolic episodes was previously found to be 7 0 episodes per 100 patients per year in all who survived the first postoperative month[15] which is insignificantly lower than that of the placebo group The difference between this total previous incidence and the rate of embolic episodes in the ASA group is also statistically significant ($p < 0.01$)

The intensity of the anticoagulant therapy was evaluated All TT values were known in 75 per cent of the patients who remained in the study until it was completed The treatment was equally strictly applied to the patients of both groups since only about 15 per cent of the individual TT values in each group fell outside a therapeutic range of 5 to 15 per cent of normal activity The consistency of the treatment was further confirmed by the distribution of TT values at the annual controls when only 22 and 25 per cent of the values in the ASA and placebo

Table IV Total observation time and incidence of arterial thromboembolic complications in the two groups of patients

	Patient groups	
	ASA	*Placebo*
Observation time patient months"	1 367	1 544
No of arterial thromboembolic episodes	2	12
Episodes per 100 patients per year	1 76	9 32
	$p < 0.01$	

Table V TT values at annual controls of patients Distribution in per cent of total number of values within each group

TT at control (%)	*Distribution (%)*	
	ASA group	*Placebo group*
< 5	3	3
6 10	30	25
11 15	45	47
16 20	11	18
21 25	6	6
> 26	5	1

group were higher than the upper therapeutic limit (Table V)

In the placebo group the TT values shortly before or at the time of the thromboembolic complications were satisfactory in 11 of the 12 cases (Table II) The anticoagulant therapy was equally intense in the 11 patients that developed such complications as in the rest of the group, since 79 per cent of their TT values at controls were within therapeutic limits

In the two patients on ASA who had embolic episodes, the TT values had been close to 10 per cent throughout the study In one of them (E S) the treatment had not been equally intense before the investigation started

The deaths and the complications that led to discontinuation of placebo are listed in Table VI Six of the patients in this group died and autopsy was performed in all but one (S U) The three with emboli who died are mentioned above including the one with a coexisting subdural hematoma (A P) In addition intracranial hemorrhage occurred in two other patients

Table VI Deaths and complications that led to discontinuation of placebo time in study and TT values shortly before or at the time of the complication

Patient	*Sex age*	*Cause of death or discontinuation*	*Death*	*Time (wk)*	*TT (%)*
S S	M, 5?	Malignant disease	+	74	
K N	M 61	Myocardial failure	+	74	
O W	M 6?	Intracerebral bleeding	+	82	5
S U	F 59	Embolia cerebri	+	16	15
A. P	M 53	Subdural hematoma embolia	+	18	9
E E	M 3?	Embolia cerebri	+	13	10
A S	M 57	Subdural hematoma		40	5
E B	M 6?	Gastrointestinal bleeding		74	< 5
H F	M 55	Gastrointestinal bleeding		36	12
A K	M 65	Epitaxis		13	9
I B	F 64	Dy pepsia		40	
H. B	M 43	Dyspepsia		5	
A R	M 65	Dyspepsia		44	
I F	F 6?	Hemolytic anemia		17	
B H	M 43	Liver cirrhosis		61	
T M	M 44	Mitral valve implantation		47	
A. F	F 44	Mitral valve implantation		6?	
E H	F 61	Mitral valve implantation		82	
H S	M 58	Lack of cooperation		6	
A. N	M 0	Lack of cooperation		52	

Table VII Deaths and complications that led to discontinuation of ASA time in stud and TT values shortly before or at the time of the complication

Patient	*Sex age*	*Cause of death or discontinuation*	*Death*	*Time (wk)*	*TT (%)*
S G	M 5?	Malignant disease	+	30	
H. M	M 51	Sudden death	+	4	14
A B	F 59	Sepsis bleeding	+	42	9
S G	F 65	Subdural hematoma		1	8
G L.	M 43	Gastrointestinal bleeding		1	9
A R	M 59	Gastrointestinal bleeding		2	12
J G	M 6?	Gastrointestinal bleeding		6	6
K I	M 6?	Gastrointestinal bleeding		24	5
K D	F 40	Gastrointestinal bleeding		34	11
U O	M 55	Gastrointestinal bleeding		40	10
H M	M 67	Gastrointestinal bleeding		43	5
H S	M 48	Gastrointestinal bleeding		45	< 5
R. H	F 60	Gastrointestinal bleeding		51	< 5
E M	M 57	Gastrointestinal bleeding		55	11
P K	M 54	Gastrointestinal bleeding		90	8
S G	M 54	Perforated peptic ulcer		5	11
M B	F 48	Subcutaneous bleeding		3	28
E J	M 59	Subcutaneous bleeding		18	15
M. H	F 55	Dyspepsia		1	
K. S	M 55	Dyspepsia		12	
K. K	M 5?	Dyspepsia		6	
J B	M 60	Dyspepsia		40	
P H	M 58	Hemolytic anemia		40	
L. J	F 59	Mitral valve implantation		99	
J L.	M ?9	Mitral valve implantation		62	
A. T	M 61	Hypertonia		8?	
E. H	F 51	Lack of cooperation		2	
B B	M 68	Lack of cooperation		18	

Table III Arterial thromboembolic complications in patients receiving ASA and anticoagulants Duration of ASA administration and TT value

Patient	Sex age	Thromboembolic complication	ASA (wk)	TT value (%)
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E S	M 36	Embolia a retinalis	48	8

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	Patient groups ASA	Patient groups Placebo
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several days[21] even infrequent ingestion of small amounts of the drug might reduce the tendency to arterial thrombus formation In spite of this the difference between the incidences of thromboembolic complications in the ASA group and in all patients previously is also statistically significant which further confirms the antithrombotic effect of the combined treatment

To our knowledge similar studies with a combination of ASA and anticoagulants have not been performed before and except for the trial with dipyridamole reported by Sullivan and associates[1] the antithrombotic effects of drugs modifying platelet function have not been tested in patients with prosthetic heart valves

Arterial thrombi are mainly composed of aggregated platelet masses and fibrin strands [2] and the platelet release reaction with subsequent platelet aggregation is an important step in arterial thrombus formation Drugs that inhibit the platelet release reaction might therefore prevent arterial thrombosis Most experimental studies have shown that administration of ASA reduces the formation of arterial thrombi but some others have failed to demonstrate this effect[30] Danese and associates[5] found that ASA given to dogs reduced the development of thrombi in arteries that were injured whereas dipyridamole had no protective effect Dragojevic and associates[8] implanted Teflon strips in dogs hearts and found that ASA administration totally prevented thrombus formation whereas dipyridamole or warfarin did not Dipyridamole has however been found to reduce the incidence of arterial thrombosis in some studies in animals

Previous investigations have demonstrated that uniocular visual loss—*amaurosis fugax*—may be caused by arterial microemboli and ASA has been reported to reduce the number of attacks strikingly Five episodes of sudden loss of vision occurred in our patients This indicates that microemboli are rather frequent in valve patients since small emboli probably give definite symptoms and can be detected only when they lodge in retinal arteries but remain undiagnosed elsewhere[3] It is therefore possible that the more vague symptoms that these patients often complain of are partly caused by cerebral microemboli

Most clinical studies with ASA as an antithrombotic agent have been done on prevention of postoperative venous thrombosis and pulmonary embolism and some effect has been demonstrated in larger series of patients[2, 36] In one study ASA did not inhibit fibrin deposition in veins as detected by scanning after [2]I labeled fibrinogen administration but the deposition could be a process not directly related to thrombosis[37] The dominant mechanism in venous thrombosis is plasma coagulation while platelets play an important role in arterial thrombus formation[22] Arterial thrombi may therefore be more effectively prevented than venous by drugs that inhibit the platelet release reaction

Myocardial infarction has been included among the thromboembolic complications in our study In patients with artificial heart valves coronary artery occlusion may be caused by thrombus formation on the valve itself either by direct extension or by embolization [3, 3] However the role of thrombosis in the pathogenesis of myocardial infarction has not been definitely settled[2, 39] and it has even been suggested that thrombosis may be a consequence rather than a cause of infarction[2, 0] The interpretation of studies on antithrombotic drugs in myocardial infarction is therefore difficult In view of this the results from two investigations that indicate some effect of ASA in the prevention of myocardial infarction are encouraging In one a significant negative association was found between aspirin intake and infarction[2] in the other the death rate 1 year after infarction was 25 per cent lower in the group of patients taking ASA than in the control group[13] The inhibiting effect of ASA on arterial thromboembolism has been confirmed by our study in ball valve patients where the pathogenetic difficulties mentioned do not exist

Some problems were encountered with the conduction of our investigation We had to continually assess whether serious complications that could possibly be ascribed to the combined treatment occurred more frequently in one of the groups which would necessitate the cessation of the trial Therefore the one of us who performed the study was informed after each discontinuation from such complications whether the patient had received Colfarit A or B but not which preparation contained ASA Since arterial thromboembolism was diagnosed without any information about the type of drug used and the records were reviewed by two of us independently the study was double blind The problems in connec

Table VIII Arterial thromboembolic complications in the third group of patients with Starr Edwards aortic ball valves those excluded from the ASA and placebo group at the start of the study or later TT values shortly before or at the time of complications

Patient	*Sex age*	*Thromboembolic complication*	*TT value (%)*
A A	M 71	Embolia cerebri	10
K K	M 58	Embolia cerebri	10
A T	M 61	Embolia cerebri	12
H B	M 43	Embolia a retinalis	21
S G	M 51	Embolia a retinalis	20
H K	M 53	Thrombus interfering with valve function	15

belonging to the placebo group One man (O W) died from intracranial bleeding and another (A S) survived a subdural hematoma that was evacuated by operation but he has considerable permanent functional disturbances Both episodes occurred at low TT values, as did one of the two gastrointestinal bleeding complications Since placebo was discontinued in 14 patients 53 remained in this group at the end of the study

Occult blood was detected in at least two of the three stool specimens from three of the patients who were still receiving placebo at the final examination The results from the salicylate level determination indicated that the patients in this group followed their instructions and strictly avoided drugs containing ASA

Three of the patients who received ASA died and the drug was discontinued in 25 others for various reasons (Table VII) Thus 47 patients were still include in this group at the end of the study One of the patients who died (H M) lived alone and was found dead outside his house The physician called for was not informed about the investigation and autopsy was not performed A 59 year old woman (A B) had a period of weakness and fever lasting for some weeks, her condition gradually deteriorated she sank into coma and died at the local hospital Autopsy revealed sepsis with bleeding in an intracranial septic focus Another woman (S G) developed a subdural hematoma without history of trauma she was operated on and recovered completely

Gastrointestinal bleeding occurred in 11 patients and was the main cause of discontinuation of ASA All these patients and the one who was operated on for a perforated peptic ulcer recovered Two of the persons with gastrointestinal bleeding had TT values below the therapeutic range and one of them (H S) had not followed the instructions given with regard to anticoagulant treatment Since the majority of the TT values before the bleeding complications during the first year of the study were below 10 per cent the doctors were advised to avoid these low values After that such bleeding occurred in only two patients (E M and P K) Occult fecal blood loss was detected in 12 patients still taking ASA at the end of the study

The plasma salicylate levels were low in only three of the patients in the ASA group After the code was broken they were contacted, and two of them explained that they had not taken the drug the night preceding the sampling of blood because of the travel to the hospital while the third had to admit some irregularities in his drug administration In the other patients in this group the mean of the salicylate concentrations was 32 3 and the range 13 6 to 56 6 μg per milliliter

In the third group of patients six arterial thromboembolic complications appeared (Table VIII) none of them severe Three of the six patients with such episodes had earlier received ASA (K K A T and S G) and one (H B) had been excluded from the placebo group The total observation time in patients not receiving ASA or placebo was 942 patient months, and the incidence was 7 64 thromboembolic episodes per 100 patients per year which is virtually the same as that of all patients until the study started

Discussion

This investigation has clearly documented that ASA combined with anticoagulant therapy is more effective in preventing arterial thromboembolism than is anticoagulant treatment alone The possible tendency toward a higher rate of such complications in the placebo group than in all patients before the study started[15] cannot be due to differences in anticoagulant therapy since this was equally intensely applied in both periods of time [15] It may better be explained by the fact that the patients included in the trial were especially instructed to avoid ASA from other sources Several patients admitted that they had occasionally taken such drugs previously Since only a small dose of ASA is necessary to inhibit platelet aggregation [1] and since the inhibition lasts for

poproteins platelet factor 3 which is important in some steps of the coagulation sequence[22] Since there is a good evidence that a number of clotting factors are adsorbed to the platelets[22] it appears that the surface of aggregated platelets is an ideal site for rapid local generation of thrombin In addition to its ability to convert fibrinogen to fibrin which is necessary in order to stabilize the thrombus thrombin is a very potent inducer of the platelet release reaction[24] It may therefore accelerate arterial thrombus formation

The inhibition of release by ASA in vitro is not complete[1] exposure of platelets to foreign material in vivo might possibly induce some extent of release aggregation and local thrombin formation despite ASA administration This may explain why arterial thrombus formation has not been completely prevented by ASA in some experimental studies In rats excessive doses of anticoagulants caused prolonged bleeding and defective platelet plug formation[3] probably because of insufficient fibrin formation whereas the primary hemostasis is not affected by anticoagulants in therapeutic doses in human subjects[3] The finding that anticoagulant treatment offers some protection against arterial thromboembolism in patients with ball valves[2] [9] indicates a role of coagulation in arterial thrombus formation The increased risk of myocardial infarction in women using oral contraceptives[61] further reflects the relation between coagulation and arterial thrombosis However one would consider ASA to be more effective than anticoagulants in preventing arterial thrombosis because of its inhibition of the release reaction which is probably due to inhibition of prostaglandin biosynthesis[6] Moreover incubation of thrombin with ASA has been found to reduce the effects of thrombin on platelets[63] indicating another inhibitory effect of ASA on thrombogenesis

When planning this study we found it difficult to exclude the possibility that arterial thrombosis might be more effectively prevented by the combination of ASA and anticoagulants than by ASA alone Therefore we regarded it unethical to stop anticoagulant treatment in any of the groups This problem will be the issue of another investigation

In conclusion the study clearly established that ASA combined with anticoagulant therapy offered a far better protection against arterial thromboembolism than did anticoagulants alone The increase in gastrointestinal complications was acceptable when compared to the antithrombotic effect achieved

Summary

Prevention of arterial thromboembolism with acetylsalicylic acid (ASA) was studied in 148 patients with single Starr Edwards aortic ball valve prostheses These patients are suitable for such a study because they have a high incidence of arterial emboli derived mainly from thrombi formed on the valves They were given either 1 Gm of ASA daily or placebo in combination with anticoagulants and were observed for 2 years Only two emboli occurred in patients receiving ASA none of them severe In the placebo group 12 thromboembolic episodes were diagnosed in 10 patients and three with cerebral emboli died in one a subdural hematoma unrelated to the embolus was found In addition one fatal and one nonfatal intracranial bleeding occurred in each group whereas gastrointestinal complications were seen more frequently in patients taking ASA

It is concluded that ASA combined with anticoagulants offered a significantly better protection against arterial thromboembolism than did anticoagulant therapy alone

Bayer AG Leverkusen West Germany provided financial support produced the tablets containing ASA and placebo and determined the plasma salicylate levels The cooperation of Dr D Loew Bayer AG is greatly appreciated. We are indebted to Prof Dr A. Torvik for the postmortem examination of the brain from the patient with intracerebral bleeding and embolus and to Mrs A L Almaas for skilled technical assistance.

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tion with the administration of the drugs were small, since the patients followed their instructions and avoided ASA from other sources, and *very few of them discontinued the medication by* themselves.

Regarding the two embolic episodes that occurred in patients receiving ASA, one cannot exclude the possibility that thrombi had been formed on the valves before ASA was instituted, since thrombus formation on artificial valves may start shortly after the implantation[15] and since "silent" thrombi have been found on valves at autopsy or on reoperation.[15] The fact that several patients with cerebral embolism had previously suffered from embolic episodes indicates that emboli in both patient groups could be derived from thrombi formed before the study started.

The distinction between cerebral embolism and intracranial hemorrhage might be difficult. Although arterial thrombosis or embolism generally are the predominant causes of larger[44] and smaller[45] cerebral infarcts, the use of ASA and anticoagulants might provoke intracranial bleeding. Therefore, strict criteria for the diagnosis of cerebral embolic episodes were necessary, with special emphasis on acute onset of the symptoms. Subdural hematomas are occasionally caused by arterial bleeding but even then the development is slightly protracted or a history of trauma can *be obtained*.[43] *In our study* the *five cases of* intracranial bleeding were all verified at autopsy or operation, and only two occurred in patients receiving ASA including the one with bleeding in a septic focus. When the numbers of cerebral embolic and bleeding complications are combined a total of only three episodes occurred in patients taking ASA, as compared to 10 in the placebo group. Thus, the addition of ASA to the anticoagulant therapy reduced the number of cerebral emboli considerably without increasing the risk of intracranial bleeding.

Anticoagulants are usually given to patients with ball valve prostheses and intracranial hemorrhage is not rarely a *serious complication*.[11,12,47,51] The bleeding tendency caused by intense anticoagulant treatment may be augmented in such patients by their disturbed platelet *function as shown by decreased* adhesiveness to glass beads[5] and slightly prolonged bleeding *time*.[53] ASA ingestion caused a marked further prolongation of the bleeding time in ball *valve patients*, possibly because of their low number of adhesive platelets.[54] Intense anticoagulant therapy combined with ASA administration might therefore have induced a strong bleeding tendency. Because of this a strict control of the anticoagulation was necessary. Although some TT values outside the therapeutic range were unavoidable, we consider the anticoagulant treatment to be satisfactory in both groups.

The relation between ASA intake and gastrointestinal bleeding is well established.[1-5] Overt as well as occult bleeding occurred more frequently in our patients receiving the drug than in the others, probably partly because of the direct effect of ASA on the gastric mucosa since this type of bleeding dominated and since a gastric perforation also developed. Bleeding episodes in other regions were quite equally distributed between the two groups. Although blood transfusions were needed in several patients none of the gastrointestinal complications were serious, and they may be considered to be an acceptable price to pay for the protection achieved against arterial thromboembolism.

The majority of all bleeding complications occurred at low TT values. This focuses interest on the role of the anticoagulant treatment, and poses the following questions: Does ASA prevent arterial thromboembolism so effectively that the *anticoagulant therapy can be abandoned* or the intensity of the treatment reduced? Would the tendency to bleeding thereby be lowered? Even if the documented antithrombotic effect of ASA combined with anticoagulants is promising, the present investigation cannot give definite answer to these questions. From our knowledge of the process of arterial thrombus formation the possible antithrombotic effect of anticoagulant therapy in addition to ASA cannot be excluded even if inhibition of the platelet release *reaction* must be considered more important in view of the *primary participation of platelets in arterial* thrombosis. The relationship between platelets *and blood coagulation* is complex. The first step is adhesion of platelets to subendothelial structures[56] or foreign material.[5] This contact triggers release of platelet constituents and ADP thereby made available induces primary aggregation of more platelets, which subsequently undergo release and irreversible aggregation, and a platelet thrombus forms.[2-4] Platelet release and aggregation expose platelet membrane phosphol-

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of Bacteroides we prefer aqueous penicillin In cases of abdominal sepsis clindamycin or chloramphenicol should be added

Corticosteroid agents Corticosteroid analogs in amounts up to 50 times those required for adrenal replacement suppress systemic reactions to endotoxin and tend to prevent non pecific cellular injury Corticosteroids also increase cardiac output and decrease peripheral arterial resistance Methylprednisolone sodium succinate in doses of 30 mg per kilogram or dexamethasone phosphate in doses of 6 mg per kilogram is administered and these doses are repeated every four to six hours When clinical signs of shock have subsided corticosteroid therapy is abruptly discontinued In most instances only three or four doses of the corticosteroid agent are administered Gastrointestinal bleeding may be a relative contraindication to treatment with corticosteroid analogs

Fluid repletion Large volumes of fluid are sequestered at sites of inflammation Substantial fluid deficits also stem from fever vomiting and diarrhea Fluid replacement is an important component of therapy Flow directed pulmonary artery catheters provide the clinician a means for monitoring pulmonary artery and wedge pressures[5] Changes in these pressures during fluid infusion are used to assess the capacity of the heart to accept the fluid load

A standard technique of fluid challenge is recommended Infusions of fluid at rates ranging from 5 to 20 ml /min for a period of ten minutes are recommended If the pulmonary artery wedge or diastolic pressure increases by more than 7 mm Hg above the initial pressure the infusion is discontinued If the pressure does not exceed the control pressure by more than 3 mm Hg after ten minutes of fluid infusion or if it decreases to less than this value over a subsequent ten minute rest period a second aliquot of fluid is administered over a ten minute period and the 7–3 *rule* is again applied This procedure is repeated during each ten minute interval until vascular volume is adequate or limits are exceeded Larger quantities of fluid may be required

Measurements of central venous pressure (CVP) also may be helpful in assessing the competence of the heart to accept a volume load The same rules apply as for the fluid challenge technique utilizing the pulmonary artery diastolic or wedge pressure except that the limiting values are 5 and 2 cm H_2O respectively In instances in which the initial pulmonary artery diastolic or wedge pressure is less than 12 mm Hg or the initial CVP is less than 10 cm H_2O respectively the rate of fluid challenge is limited to 5 ml /min

For plasma volume expansion combinations of physiological salt solution and plasma protein solutions are recommended However when colloid osmotic pressure is reduced to values of less than 18 mm Hg fluid challenge is best begun with solutions of 5 per cent normal human serum albumin or plasma protein fraction[6,7] Dextrans may also be used to increase vascular volume although these substances may provoke allergic reactions and abnormalities in blood clotting Administration of blood is reserved for patients in whom a critical reduction in red cell mass has been demonstrated

Vasoactive drugs If augmentation of intravascular volume does not reverse the signs of peripheral vasoconstriction treatment with the alpha beta adrenergic agonist dopamine hydrochloride or the beta adrenergic isoproterenol may be considered Dopamine increases myocardial contractility and increases visceral including renal blood flow Dopamine may be used for treatment of shock in patients in whom there is concurrent myocardial failure due to coronary insufficiency We suggest that dopamine be used in amounts that maintain arterial pressure approximately 20 to 30 mm Hg less than normal for that patient to avoid excessive arterial vasoconstriction Dopamine is administered in amounts that usually *range from* 2 μg to 5 μg/Kg /min but may be increased up *to* 20 μg/Kg /min

Isoproterenol is a potent myocardial stimulant and decreases venous pooling thereby producing striking *increases in cardiac* output However this agent has the potential risk of inducing tachycardia and cardiac arrhythmias and increases metabolic rate and therefore the systemic requirements *for* oxygen Isoproterenol should be used only after the plasma volume has been fully *repleted* so as to minimize its hypotensive action *Doses usually* range from 0 5 μg to 5 0 μg/min , but may be increased up to 10 0 μg/min Neither dopamine nor isoproterenol are of proven benefit *with respect* to ultimate survival accordingly their use *should* be regarded as only a temporary expedient

Fundamentals of clinical cardiology

Bacterial shock

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The majority of cases of bacterial shock are caused by Gram negative enteric bacilli Bacteremia is rarely complicated by shock in persons under the age of 40, except in women during pregnancy and in neonates If patients with septic abortion are excluded, bacterial shock is more frequent in men than in women reflecting the higher incidence of urinary tract infections in older men Diabetes, chronic liver disease and blood dyscrasias predispose to bacteremia and shock Bacteremia with shock is usually precipitated by a manipulative procedure Treatment with corticosteroids immunosuppressive drugs, and antimetabolites predispose to sepsis

Pathophysiology

When hypotension appears during Gram negative bacteremia the patient frequently is seen with fever and warm extremities During this early pyrogenic phase of acute circulatory failure arterial vasodilation typically predominates together with an increase in pulse pressure and cardiac output [1] This is followed by arterial vasoconstriction and a reduction in cardiac output A substantial portion of the blood appears to be pooled in the venous capacitance bed reducing the effective blood volume Tissue oxygenation is curtailed and blood lactate levels rise

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Clinical manifestations

Gram negative bacteremia typically begins with a shaking chill followed by fever between two and 24 hours after mechanical manipulation or surgery Impaired mental status may result from reduced cerebral perfusion Vomiting and diarrhea are frequent findings Leukopenia and thrombocytopenia may accompany the onset of shock, followed by leukocytosis Serum transaminase levels reflect the cellular injury of shock Clearance of amylase is reduced and serum amylase values may be considerably elevated Abnormalities of the ST segment and T wave reflect a reduction in coronary perfusion

Treatment

Antibiotics Before antibiotic therapy is started specimens of blood urine sputum and wound exudates are obtained for bacteriological culture and sensitivity studies At least three blood cultures are taken If a primary site of infection has been recognized and the organism previously recovered antibiotic therapy is selected accordingly

Prior to the time when results of bacteriological culture and sensitivity studies are available antibiotic treatment with a bactericidal agent is nevertheless immediately required On an empirical basis gentamicin sulfate is currently the drug of choice [3] Tobramycin may be used as an alternative to gentamicin The fact that renal function is impaired in patients with bacterial shock must be taken into account once the loading dose has been administered Serum creatinine and when feasible creatinine clearance provide a basis for estimating the amount and frequency of subsequent doses of antibiotics Determination of antibiotic levels in the serum may also be used to guide antibiotic dosage

In patients with concurrent infections due to Gram positive organisms and respiratory strains

Cardiac pacing and pacemakers IV Threshold of cardiac stimulation

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Comprehension of the threshold of cardiac stimulation is basic to pulse generator and electrode design selection of a power source for the pulse generator and proper implant technique The selection of pulse generator output is directly affected by the threshold needs of the electrode A number of energy sources presently used and for which prolonged longevity is claimed would be no better than older sources or totally inadequate at output levels required for electrodes considered standard five years ago The best balance of power source longevity and the requirements of cardiac stimulation can be achieved by knowledge of the threshold of stimulation the minimum stimulus required to initiate a cardiac depolarization

All of the following factors affect the threshold

1 Position of the *electrode relative* to stimulatable tissue
2 Maturity i e duration of the electrode in one position
3 Pulse duration
4 Whether the electrode is unipolar or bipolar i e anodal size
5 Electrode surface area and shape
6 Anodal or cathodal stimulation
7 The *metal* of which the electrode is fabricated
8 Drugs and electrolyte balance

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Position of the electrode

This factor is directly under surgical control during pacemaker implant Intraoperative selection of the best position is basic to the success of continued cardiac stimulation Each electrode has a characteristic threshold within which virtually all well placed implants will fall only patients with severe metabolic imbalance or areas of fibrotic myocardium will have higher thresholds The voltage and current thresholds increase rapidly with distance between the electrode and excitable myocardium[1] so that a satisfactory placement technique is mandatory As a layer of non stimulatable tissue normally forms as the electrode matures effective electrode size increases as the separation from the metal surface to sensitive tissue increases If separation from viable myocardium during initial placement is too great the threshold of the maturing electrode will rise inordinately

Maturity

Electrode threshold during the implantation procedure is termed *acute* Once threshold has stabilized several weeks or months after implant it is *chronic* During the interval between as the electrode matures threshold is labile rising to a peak about a week after implant and then declining progressively to stabilize at a level *2 to 3* times above the acute

The effect of the maturing *process* varies inversely with electrode size so that smaller *more* efficient electrodes increase threshold *more* than larger electrodes For example 8 mm surface area ball tip electrodes have *thresholds four times higher* chronically than acutely For electrodes of larger surface area this chronic to acute ratio decreases so that an electrode of 50 mm

Neither levarterenol (Levophed) bitartrate nor *metaraminol bitartrate (Aramine)* is *indicated for* routine treatment These vasopressor agents may increase peripheral vasoconstriction and further compromise effective blood flow

Body temperature Fever may be controlled with a cooling blanket There is no evidence that reduction of temperature to subnormal level is advantageous Chilling should be avoided since it greatly increases oxygen requirements

Acidosis Acidosis is most often due to a failure of tissue perfusion with accumulation of acid metabolites Measures that improve flow, rather than the administration of sodium bicarbonate, constitute rational treatment

Disseminated intravascular coagulation Gross bleeding due to consumption coagulopathy is encountered in only the exceptional patient When this complication is substantiated anti coagulation with intravenous injection of heparin sodium in amounts ranging from 3 500 to 5 000 units every four hours is indicated

Respiratory management Continuing close attention to respiratory function is mandatory In a majority of patients progressive perfusion failure is followed by respiratory failure Serial measurements of arterial blood gases provide the physician with objective criteria for assessing both the oxygen requirement and the need for endotracheal intubation and mechanical ventila tion

Surgical For the management of bacterial shock surgical treatment may be indicated for control of the bacterial infection It is essential that abscesses be promptly drained and that grossly infected tissues be surgically removed

Summary

Bacterial shock due to Gram negative bacilli is best managed by prompt control of the infection with appropriate antibiotics and surgical drainage or excision Corticosteroids for purposes of controlling systemic reactions to bacteria and their toxins constitute adjunctive therapy Vol ume repletion and respiratory support may be of the greatest importance for temporary support of these critically ill patients Vasoactive drugs including dopamine and isoproterenol should be used very sparingly and only as very temporary expedients

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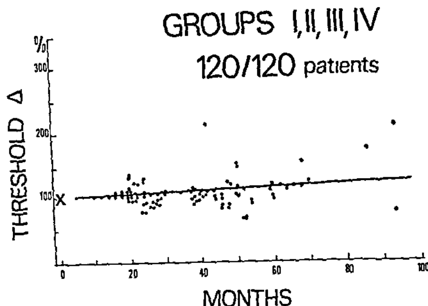


Fig 1 Th scatter of chronic thresholds in 120 patients followed over five years. X is the first threshold for all patients representing 100 per cent of the first chronic threshold All subsequent thresholds for each patient are compared to the 100 per cent point Despite the scatter for some patients the upward trend is 2 4 ± 0 7 per cent per year for the entire group

The second group of 297 patients showed no progressive threshold increase beyond that seen in the immediate postoperative period during a follow up period of less than five years It thus seems that the assumption of threshold stability is reflected in experience

Pulse duration

Threshold varies as a function of impulse duration and the direction of this variation is dependent on the parameter measured The strength-duration curve is a major basis for understanding cardiac stimulation threshold *Current voltage charge* (the product of current and time) and *energy* (the product of current voltage and time [E = IVT]) all vary as a function of pulse duration Conservation of the capacity of the pacemaker power source and its minimum consumption must be sought and accomplished without loss of safety margin

Current The current flow at threshold from a constant current generator is parallel to the abscissa from about 1 0 msec onward (Rheobase) Threshold values rise as pulse duration shortens (Fig 2)

Volts Rheobase is reached at 1 0 msec at shorter durations threshold rises (Fig 3)

The two derived functions *charge* and *energy* show a different pattern *Charge* is perhaps the most useful single function as it describes threshold in the same terms in which chemical battery capacity is measured (milliampere hours or ampere hours) and its consumption is inversely related to battery longevity *Charge* expended at threshold decreases with shortened pulse duration as the decline in time is far more rapid than increase in current flow (Fig 4)

The most efficient pulse duration for energy consumption lies between 0 25 and 1 0 msec where the curve is flat and parallel to the abscissa At shorter and longer pulse durations energy consumption at threshold rises (Fig 5) As the voltage output of a chemical battery is fixed reduction of voltage supplied to the electrode is a less efficient method of conservation of capacity than reduction of pulse duration or current flow

Impedance Impedance to the flow of electrical energy varies directly declining progressively from longer to shorter pulse duration (Fig 6)

Electrode polarization[13] is a build up of charge which opposes further flow of current It is manifested on an oscillogram (Fig 7) as a rising voltage during a constant current stimulus

Table I Acute and chronic electrode threshold for varying sizes of electrode surface area

Surface area (mm^2)	Current (mA)		Current density (mA/cm^2)		Chronic/Acute ratio
	Acute	Chronic	Acute	Chronic	
8	0 244 ± 069	0 91 ± 0 520	2 80	11 4	4 06
12	0 376 ± 113	1 17 ± 0 250	3 13	9 75	3 12
28	0 688 ± 259	2 08 ± 0 690	2 46	7 43	3 02
50	1 54 ± 560	3 62 ± 2 09	3 08	7 24	2 35

Table II Minimum output characteristics of different pacemakers

Manufacturer	Model	Volts	Minimum	
			Current (mA)	Pulse duration (msec)
Cordis	162C D	1 15	2 3	1 2
Cordis	143N	6 5	3 0	1 0
Medtronic	5931 5961	5 4	10 0	0 05

surface area has a chronic/acute ratio of only 2 35 Despite this phenomenon the lower acute threshold of small electrodes is more significant than their higher chronic to acute threshold ratio An 8 mm² electrode has a chronic threshold of 0 91 ± 52 mA while the 50 mm² electrode has a chronic threshold of 3 62 ± 2 09 mA, a wholly unacceptable threshold at any time during the development of pacemaker technology (Table I)

After the initial maturation process indefinite electrode threshold stability can be anticipated All efforts to construct pulse generators with prolonged longevity are based on the implicit assumption that such threshold stability exists Though some reports[9,10] have suggested that progressive threshold increase occurs, such an increase is an uncommon occurrence The reasons for replacement of a chronically functioning electrode are

1 Irreparable lead fracture
2 Irreparable insulation failure
3 Infection
4 Electrode corrosion caused by a direct current leak from the pulse generator a defect possible even in some modern designs[11]
5 The uncommon progressive threshold rise above the output capacity of a generator

The last is almost always caused by undetected poor initial placement, as repositioning either a transvenous or myocardial electrode usually results in permanent stability

Long term electrode threshold stability was demonstrated by analysis of two specific groups[12]

1 All patients with the same electrode (with all follow up by the authors) implanted at least five years with two or more threshold determinations beyond that at implant

2 Those patients implanted with pacemakers the output of which was non invasively variable, so that threshold could be ascertained or with generators of output so low that any substantial increase would be reflected promptly in cessation of pacing There were 120 patients in the first group and 297 in the second (Table II)

The group of 120 had a total of 380 chronic data points Scatter was present but four subgroups were readily discernible A *stable* subgroup of 43 per cent who demonstrated a progressive threshold increase of +0 7 per cent ± 0 7 per cent per year, a subgroup of 17 per cent with a *progressive decline* of threshold of −5 0 per cent ± 0 6 per cent per year an over all stable subgroup of 22 per cent, but with individual *wide variability* of the threshold points about the mean and an upward slope of +1 9 per cent ± 1 3 per cent per year, and a subgroup of 19 per cent with an *increase* of +14 per cent ± 2 4 per cent per year Thus 81 per cent of electrodes have stable thresholds with an over all slope of 0 4 per cent ± 0 6 per cent per year and the entire group an upward slope of 2 4 per cent ± 0 7 per cent per year Though it has not been possible to identify in advance those electrodes which will have rising thresholds they represent only a fifth of patients and would nevertheless require 6 to 7 years for threshold rise to exceed pacer output (Fig 1)

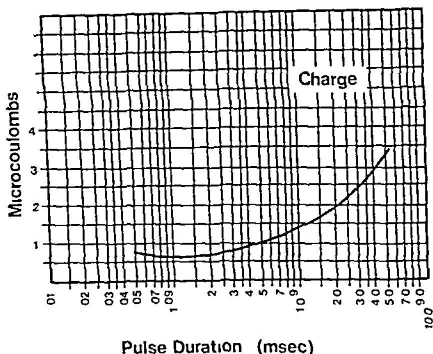


Fig 4 Charge at threshold decreases at short pulse durations. As this is the most accurate measure of expenditure of capacity of a chemical battery it is most valuable in analyzing battery longevity (Cordis continuous lead—chronic) Semi log scale

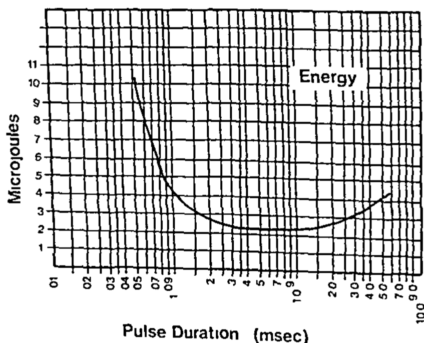


Fig 5 Energy rises at long and short pulse durations. It is lowest from about 0.25 to 1 0 msec (Cordis continuous lead—chronic) Semi log scale

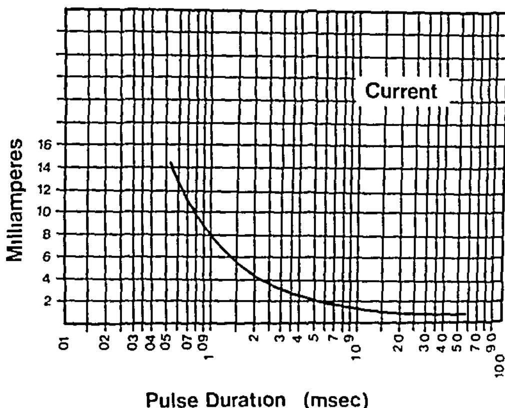


Fig 2 Current at threshold increases at short pulse durations (Cordis continuous lead–chronic) Semi log scale

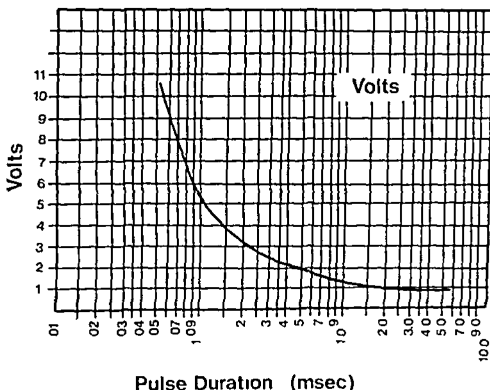


Fig 3 Voltage at threshold increases at short pulse duration (Cordis continuous lead–chronic) Semi log scale

increasing with pulse duration and current density but reaching a maximum which is specific for each metal

Unipolar vs bipolar

The terms 'unipolar' and bipolar refer to the presence of the cathode and anode within the heart (bipolar) or the cathode only intracardiac and the anode remote in the body The negative terminal (cathode) must be stimulating in all instances and threshold is a function of cathodal characteristics (except as indicated in Cathodal and Anodal Pacing) The current threshold for stimulation is identical for both unipolar and

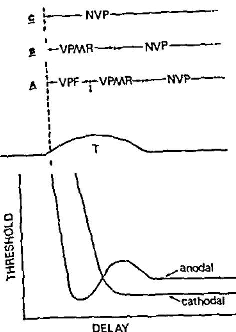


Fig 8 Three types of myocardial response to suprathreshold stimuli after the refractory period are observed A The *vulnerable period* for *fibrillation (VPF)* followed by one for *multiple responses (VPMR)* followed by the *non vulnerable period (NVP)* B Stimulation early in the excitable period produces *multiple responses* followed by a non vulnerable period C Some animals are non vulnerable to arrhythmias and a single stimulus produces a single response The cathodal and anodal excitation thresholds at different delays during the cardiac cycle *(strength interval curves)* are also shown

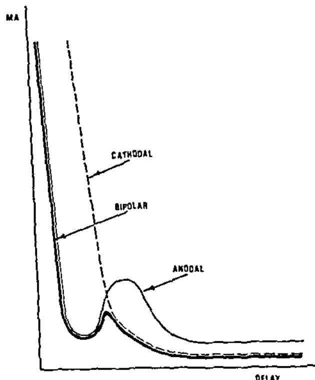


Fig 9 Relationship between cathodal anodal and bipolar strength-interval curves when the cathode and anode are of *equal surface area*

effective electrode size and corrsponding thresh olds below the apparent present limits

Anodal and cathodal stimulation

In the previous sections threshold of stimula tion was determined during diastole when ventricular sensitivity had returned to a stable level before another QRS complex During that period the myocardium is more sensitive to cathodal than to anodal stimuli and for a constant current stimulus equally sensitive to cathodal and bipolar stimuli Cardiac sensitivity to stimulation changes significantly during and immediately after the QRS complex during the relative refractory period The phenomenon of pacemaker induced ventricular fibrillation in which the stimulus falls into the vulnerable period of the cardiac cycle has been observed during bipolar stimulation [7] in all published instances but one[1] and is related to the anode of a bipolar electrode

The threshold for such an event decreases during myocardial ischemia infarction metabolic imbalance and drug intoxication [9, 20] As com pletely satisfactory pacemaker sensing of all ventricular foci conducted and idioventricular especially during those conditions has not yet been fully attained the problem of competition has not been eliminated Competition between premature ventricular contractions and a bipolar stimulus is especially problematic during bipolar temporary pacing following acute myocardial infarction Most temporary pacing is bipolar though perhaps half of implanted pacing is unipolar cathodal

In experimental canine cardiac stimulation during ischemia at outputs which approximate those of commercial cardiac pacers three distinct patterns follow the absolute refractory period [9]

1 Some animals are *non vulnerable* to ar rhythmia (NVP) and a single stimulus (anodal or cathodal) produces a single response *(NVP = non vulnerable period)*

2 In others the initial sensitivity produces *multiple ventricular response (VPMR)* to a single stimulus followed by a non vulnerable

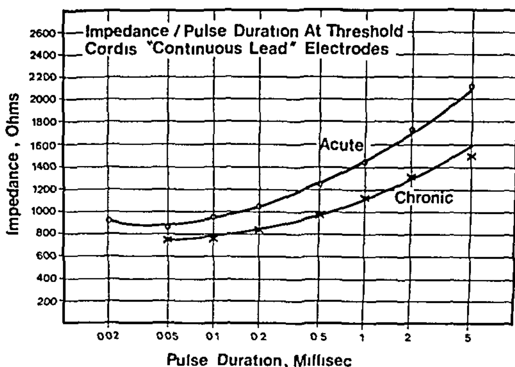


Fig 6 Impedance to electrical flow is lessened at shorter pulse durations Semi log scale

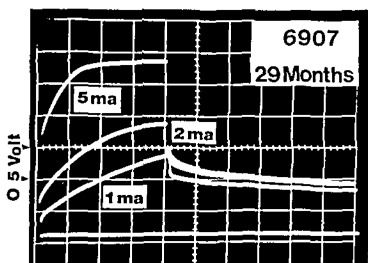


Fig 7 Voltage across a 29 month old platinum-iridium unipolar endocardial electrode (Medtronic 6907) as 2 msec constant current cathodal pulses of 1 2 and 5 mA are passed

bipolar electrodes[14] The voltage threshold is usually higher for bipolar pacing As the anode in bipolar electrodes may be the same size as the cathode or only somewhat larger a long wire from pulse generator to the intracardiac anode increases the electrical resistance The small anode increases polarization and the small anodal area exposed to the tissue surface increases the tissue resistance to current flow Overcoming these resistances requires a higher voltage In unipolar pacing the anode is usually the case of the pulse generator and may be 1 000 times larger than the cathode obviously a low resistance pathway In either event, the difference in voltage threshold is small with clinically available electrodes

Electrode surface area

The surface area of stimulating electrodes is directly and linearly related to the current threshold of stimulation Though the shape of the stimulating surface plays a role[4] its clinical significance is not clear Smaller surface area electrodes have lower *current* and *charge* thresholds than do larger electrodes and the current density threshold (mA /mm) remains relatively constant over a wide range of surface areas Voltage threshold also decreases with surface area though not as greatly as do current and charge These phenomena exist both at implant (acutely) and chronically (Table I)

The chronic to acute threshold ratio depends upon the size and shape of the electrode and the thickness of the non excitable fibrous tissue which separates the electrode from the excitable myocardium Spherical electrodes have the highest chronic threshold factor and cylindrical electrodes have the smallest[6]

An electrode of surface area of as low as 4 mm^2 has been used clinically and has been successful though smaller electrodes may have corrosion problems Novel designs such as the higher impedance DCD[15] electrode and the postulated dielectric electrode[16] represent attempts to reduce

creasing anodal surface area by the use of unipolar cathodal stimulation by a decrease in pulse generator output and by the use of shorter pulse duration for cardiac stimulation (Fig 12)

Metal for electrode fabrication

The characteristics required for pacemaker electrodes are

1 Electrochemical inertness
2 Non toxicity
3 Resistance to electrolytic destruction
4 Low electrical resistance

The electrode should not go into solution during passage of an electric current at least at the conventional pulse duration and output levels for cardiac pacing and any salt formed during pacing should be non toxic If a metal cathode meets these criteria but not as an anode then it may be used only for unipolar pacing Three metals have been successfully used for permanent pacing

1 Platinum with 10 per cent iridium
2 Elgiloy an alloy of cobalt iron chromium molybdenum nickel and manganese
3 A silver and stainless steel combination

The threshold is a function of the reactivity of the metal and the over voltage developed during passage of a current for cardiac stimulation The more noble a metal the lower will be both this over voltage and the voltage and current pacing threshold Platinum-iridium has consistently lower thresholds than the more reactive metal Elgiloy[2] Nevertheless both metals have been quite successful for long term pacing and the difference in threshold is inconsequential as a practical matter

Drug administration and electrolyte balance

Changes in electrolyte concentration have an effect on stimulating threshold Administration of potassium chloride in Ringer s solution consistently though briefly reduces threshold by as much as 20 to 40 per cent[3] while potassium in combination with insulin increases threshold by 17 to 30 per cent Hypertonic (3 per cent) sodium chloride increases threshold by 50 to 60 per cent and calcium gluconate has a slight lowering effect An increase in Po has little effect a slight decrease increases threshold and a marked hypoxia reduces threshold An increase in Pco_2 increases threshold and a decrease has little effect[2]

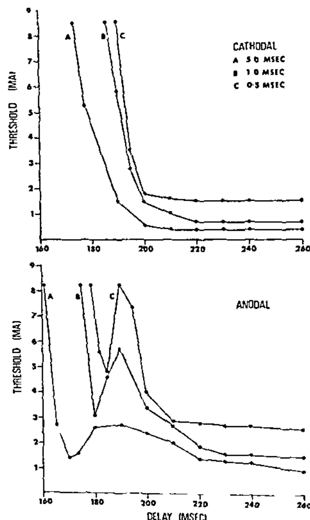


Fig 12 Unipolar cathodal and anodal strength interval curves determined with a Cordis 4F electrode utilizing 5 0 1 0 and 0 5 msec duration pulses The absolute refractory periods are longest with the shortest duration pulses

The glucocorticoids methylprednisolone and prednisone and epinephrine and ephedrine decrease threshold[24] Isoproterenol aldactone and propranolol and verapamil quinidine ajmaline all increase threshold[1] Digitalis morphine lidocaine and procainamide in the usual therapeutic dose range have little effect[3] Nevertheless drug administration has little sustained effect on threshold and need not be considered as a cause for threshold increase during cardiac pacing or relied upon as an effective means of threshold reduction Even where a pronouced immediate effect occurs sustained drug administration is accompanied by gradual return to the pretreatment baseline over several hours The major problem that can occur is the acute loss of

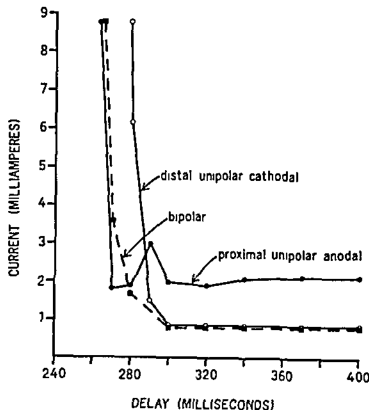


Fig 10 Unipolar cathodal *(at distal site)* unipolar anodal *(at proximal site)* and bipolar strength-interval curves determined in a patient with a Cordis temporary 4F electrode Note that the anodal and bipolar absolute refractory periods are equal and shorter than the cathodal refractory period

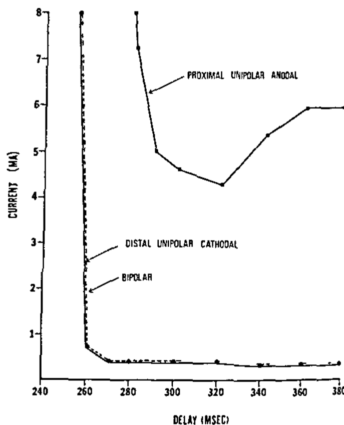


Fig 11 Typical unipolar cathodal *(at distal site of electrode)* unipolar anodal *(at proximal site)* and bipolar strength-interval curves in a patient with an acute Medtronic 6901 bipolar electrode (distal surface area = 11 mm proximal surface area = 48 mm ²) Note that the bipolar and unipolar cathodal refractory periods are equal

period, (VPMR = *vulnerable period for multiple responses*)

3 In still others the earliest response will be that of *ventricular fibrillation* followed by the *vulnerable period for multiple responses* and then the *non vulnerable period* (VF = ventricular fibrillation)

Sensitivity to anodal stimulation occurs earlier than cathodal after the absolute refractory period and because of the phenomenon of the anodal dip sensitivity is greater for a brief time during the vulnerability periods for multiple responses or VF than it *ever* is to cathodal stimulation In order to stimulate early with the cathode a much higher stimulus level is required and it is effective only well *after the beginning of anodal sensitivity* (Fig 8)[2] The anodal refractory period thus is shorter than the cathodal and if the electrode stimulating surface areas are equal the bipolar refractory period and consequent ventricular vulnerability will equal the anodal so that a bipolar or anodal stimulus can initiate an arrhythmia over a greater portion of the cardiac cycle and at a lower threshold than can a cathodal stimulus (Fig *9) The bipolar threshold* equals the lower of the anodal or cathodal thresh*old* so that early excitation is possible[23] A variety of other factors is important surface area of the *two poles and the proximity of the anode* to sensitive tissue Some widely used electrodes for temporary pacing commonly have *equal* size anode and cathode while those for permanent pacing formerly had that relationship but the cathode in present day electrodes is smaller than the anode often by a ratio of 6 or 7 to 1

In clinical determination of the strength interval curve of stimulation in those with *temporary* electrodes of equal surface area, the anodal and bipolar refractory periods were equal *and shorter than cathodal in about half the* patients (Fig 10)[4] In the remainder the cathodal and bipolar refractory periods were equal In those with newly implanted permanent bipolar electrodes or those chronically pacing and with an anodal surface area 4 to 5 times cathodal cathodal and bipolar refractory periods were equal in *90* per cent *(Fig 11)* Patients with temporary electrodes were far more susceptible to *arrhythmia than those with permanent elec*trodes Such susceptibility is decreased by in

Culture negative bacterial endocarditis confirming the diagnosis

The positive blood culture is the most definitive laboratory test for confirmation of the diagnosis of bacterial endocarditis However this disease must not be discarded from the differential diagnosis simply because routine blood cultures fail to demonstrate growth. The search for phagocytic reticuloendothelial cells rheumatoid factor activity and teichoic acid antibodies has on occasion lent considerable support to the subsequently confirmed diagnosis of bacterial endocarditis in patients with negative blood cultures This report outlines additional studies which are available to the physician who is desirous of confirming a presumptive diagnosis of bacterial endocarditis

Intraleukocytic bacteria can be demonstrated in concentrates of venous blood from approximately 50 per cent of patients with bacterial endocarditis. More important however the proper examination of leukocyte monolayers can confirm the diagnosis of bacterial endocarditis in patients with negative blood cultures

In a comparative study performed in patients with subacute bacterial endocarditis the incidence of positive cultures derived from bone marrow specimens exceeded that of the peripheral blood Unfortunately this investigation has not received the emphasis it deserves

Several reports affirm the value of hypertonic media with or without enrichment with serum plasma or ascitic fluid for the isolation of both conventional and cell wall-defective bacterial variants in patients with negative blood cultures and a clinical syndrome consistent with endocarditis As aberrant bacterial forms are susceptible to currently available antimicrobial agents and are capable of reverting to the parent form the isolation of these organisms has important therapeutic implications. In addition unusual thiol requiring variants of streptococci which require special media for isolation have been incriminated in bacterial endocarditis.

Echocardiography has proven to be a safe and effective procedure to detect some of the bacterial vegetations, the hallmark of bacterial endocarditis on the aortic and mitral valve Diagnostic ultrasound combined with phonocardiography has confirmed the presumptive diagnosis of culture negative bacterial endocarditis complicated by acute aortic regurgitation Gallium 67 myocardial imaging has also been found to be a useful technique for detecting bacterial endocarditis when blood cultures are consistently negative

Cardiac catheterization is a potentially dangerous procedure for patients with bacterial endocarditis and serious arrhythmias and dislodgment of vegetations have resulted from this diagnostic method Catheterization however can determine the site of infection in patients with bacterial endocarditis by obtaining blood for culture from the infected focus, and represents the most definitive procedure for documenting culture-negative endocarditis involving the right side of the heart

Untreated bacterial endocarditis is a lethal disease Techniques are available for making the definitive diagnosis even when blood cultures demonstrate no growth Their use should be increased

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pacing during severe electrolyte imbalance The best method of correction is prompt restoration of electrolyte balance

Cardiac stimulation is via cathodal and anodal electrodes with the cathode determining the crucial stimulation factors Short pulse duration and small electrode surface area promote efficient stimulation and when well placed, chronic threshold remains permanently stable The effects of drugs and electrolyte balance acutely on threshold are small and evanescent The entire basis of cardiac stimulation physiology, and technology is related to the threshold behavior of the cardiac electrode

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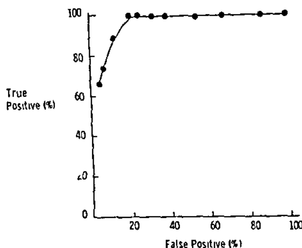


Fig 1 Case finding u ing plasma renin activity for detection of surgically correctable renovascular hypertension Each point was obtained by taking an arbitrarily selected plasma renin value to discriminate surgically correctable cases Thus the extreme right hand point was obtained by taking a value of 0 ng /ml /hr the point of inflection using this parti ular assay is 4 ng /ml /hr

While the use of plasma renin measurement has been discussed extensively over the years much of the debate has been irrelevant or misleading Any screening procedure can only be evaluated in relation to the disorder and the context in which it is being studied False positives in this screening situation simply result in a negative pyelogram while even the occasional false negative does not have the disastrous implica tions of a false negative in screening for malignancy Few single laboratory procedures lead to 100 per cent detection of a disorder and even fewer allow one to proceed immediately to treatment The background group against which patients are being screened also needs more careful consideration than has always been gi en to it This population does not consist of normotensive subjects or even normotensive subjects exposed to diuretic or dietetic stimulation of renin secretion Such a normal range is inapplicable and a demonstration that some patient with renovascular hypertension have values within this range does not negate the value of the measurement and is perhaps a trifle naive We wish to select patients from a group of individuals with essential hypertension and within this group plasma renin activity has a quite different distribu tion and range of values compared with normal subjects The response to stimulation is also of course different in normal and hyperten ive subjects. If an equally critical approach could be used in the application of this assay procedure as that which has been devoted to its development a substantial saving in resources could probably be achieved

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Preoperative deep vein thrombosis in patients with gastrointestinal disease

The occurrence of postoperative deep vein thrombosis was first described by Strauch in 1894 and it was long believed that venous thrombosis developed about the seventh postop erative day With the introduction of the I fibrinogen test it has been suggested that thrombus is established by the first postoperative day in the majority of cases and it is now widely a cepted that postoperative venous thromboem bolism starts at or about the time of operation

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Renin measurement in detecting surgically correctable renal hypertension

The extensive scientific expertise which has been invested in the development of laboratory and radiological investigations has not always been equally utilized in the application of these investigations There is a natural enough tendency for concentration to be focused upon the scientifically interesting which is not always synonymous with the clinically important When Goldblatt and co workers first described a method for the consistent production of hypertension in dogs by means of renal ischemia it was hoped that the key to hypertension in man had been found It soon became apparent that this was not the case and that the majority of hypertensive patients showed no evidence of renal ischemia Nevertheless the rat or the dog with renal ischemia proved to be valuable models for studying changes associated with the early development of hypertension which is difficult to observe in man Laboratory studies of renal hypertension have added tremendously to our understanding of the pathogenesis of the disorder at the same time they have led us to overemphasize the clinical importance of renal ischemia Furthermore even in published work on essential hypertension in man it is mandatory to include evidence that renal disease has been excluded Nevertheless the exclusion of a renal cause for hypertension involving some combination of intravenous pyelography renography and arteriography is a most traumatic time consuming and expensive exercise in the work up of hypertensive patients While radiological abnormalities of the renal tract are revealed in about a fifth of patients investigated the clinically relevant statistic is the proportion of patients with *surgically correctable* renal hypertension The incidence of this entity is much lower although patient selection clearly plays a critical role in determining its magnitude While values as high as 5 per cent have been recorded other groups have recorded values of 1 per cent 0 9 per cent [?] 1 3 per cent and even less The yield is therefore very small the rewards are by no means unequivocal Surgical treatment has its own morbidity mortality and failure rate and a certain proportion of patients with renovascular hypertension will be better off with medical than with surgical treatment An important recent study based on published data attempts to analyze the outcome of surgical as opposed to medical treatment of patients with renovascular hypertension The results indicate that more such patients survive as a result of medical than surgical treatment although there was a slightly higher incidence of non fatal vascular accidents in the medically treated group The source of the data probably prejudices the study against surgery but this work does indicate the equivocal nature of the return resulting from intensive screening for renovascular hypertension

Two alternative policies are available The first is to abandon intensive radiological screening in all but a few selected high risk patients—i e young patients patients with a very high blood pressure and advanced retinopathy patients with clinical features suggesting a diagnosis of renovascular hypertension and individuals who are known to comply poorly with a medical treatment regime

The alternative policy is to use other screening procedures Here there are two possibilities The use of the angiotensin antagonist sarco ine 1 alanine 8 angiotensin II is at present under study and early results are encouraging However both severe pres or and depressor responses have been recorded While the frequency of such hazards is clearly low the risk becomes substantial when considered in relation to the numbers of patients involved and the marginal benefits accruing from detection

The second possible screening procedure is measurement of plasma renin This is generally elevated not merely in renovascular hypertension but in about 15 per cent of patients with essential hypertension so that radiological study is still indicated in subjects with a high plasma renin level It is possible to assess the precise value of plasma renin measurement by arbitrarily taking a series of values as the cut off point for diagnosing renovascular hypertension and assessing the number of patients correctly diagnosed (true positives) and the number of patients incorrectly diagnosed (false positives) With progressively higher values for the plasma renin activity cut off point the number of false positives declines until a point is reached at which patients with renovascular hypertension are missed (i e the true positive rate falls below 100 per cent) This analysis has been carried out on pooled data for our unit and that published by Vaughan and colleagues since an identical assay is used by both units with closely similar 24 hour sodium PRA nomogram The resultant analysis suggested that it was possible to obtain 100 per cent yield of true positives with a 20 per cent false positive rate by selecting an appropriate cut off value (Fig 1)

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Of cardiac arrest and sleep

A study of patients who have had cardiac arrest has shown that patients do not dream or have nightmares during the cardiac arrest and they remember nothing When resuscitated they awaken spontaneously This is true for patients who had Stokes Adams attacks or who had a true syncope (not a hysterical faint) In these patients either th circulation to the brain is arrested or cerebral circulation is markedly reduced During natural sleep the cerebral circulation is intact The sleeping person dreams and can be awakened He periodically turns in normal fashion and with normal frequency These simple bedside observations indicate that active intact cerebral circulation is necessary for natural sleep dreaming moving periodically during sleep and for the ability to be awakened or aroused in a normal manner On the other hand with cerebral circulatory arrest none of these physiologi phenomena are possible and the patient is in a mental or cerebral state of dead sleep or nothingness He will awaken only if cerebral circulation is reestablished *prior to* irreversible brain damage Thus the presence or absence of *adequate blood flow* to the brain makes the difference in brain function when a patient is in a state of unconsciousness due to natural normal sleep as opposed to when he is unconscious *due to cardiac* and cerebral circulatory arrest In the latter state he cannot dream since dreaming is a functional state which requires blood supply to the brain

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Various therapeutic regimes have been shown to be of value in the prophylaxis of both peroperative deep vein thrombosis and of postoperative pulmonary embolism [5] However, while these forms of treatment are effective in reducing the incidence of thromboembolism associated with surgery none are universally successful It is possible that the failure of such prophylactic treatment to completely prevent venous thrombosis occurring at or near the time of operation and subsequent postoperative pulmonary embolism is due to the presence of established deep vein thrombus prior to the patient undergoing operation

It is well recognized that patients with acute medical illnesses are at as great a risk of venous thromboembolism as surgical patients and it is not uncommon for ill medical patients to require surgery Futhermore patients with certain diseases notably malignancies and inflammatory bowel diseases are particularly susceptible to thromboembolism even in the absence of surgical treatment Indeed patients with malignant disease undergoing operation have a very high incidence of deep vein thrombosis most of which can be detected by the first postoperative day unlike patients with benign conditions in whom thrombus develops later in the postoperative period Although prophylactic measures significantly reduce the incidence of venous thrombosis in patients with benign disease undergoing surgery most have been reported to be ineffective in patients with malignancy [11] It may well be that some patients undergo surgery with deep vein thrombus established in the preoperative period and the subsequent effects of surgery encourage extension and propagation of clot thus rendering prophylactic measures less effective when introduced at the time of operation

We have recently studied a group of 50 patients with gastrointestinal disease prior to surgery for evidence of established deep venous thrombosis These patients were all over 30 years of age and were admitted to hospital more than four days prior to surgery for either investigation or preparation for operation Patients with both benign and malignant conditions were studied and some received preoperative intravenous feeding All patients were encouraged to remain ambulant prior to operation and none were confined to bed The I fibrinogen test was performed daily for 6 to 8 days immediately prior to operation and positive results were confirmed by bilateral ascending phlebography Eleven of these patients developed a positive preoperative I fibrinogen test and the presence of thrombus was confirmed venographically in ten patients In four of these ten patients thrombus extended above the level of the knee and one of these patients subsequently died from postoperative pulmonary embolism despite anticoagulation with heparin Continued observation in the postoperative period revealed a further nine positive [2] I fibrinogen tests of which six patients had thrombus confirmed by venography The over all incidence of deep vein thrombosis in this study was 32 per cent Analysis of the patients developing preoperative deep vein thrombosis showed that those at greatest risk were patients with malignant disease who received preoperative intravenous feeding 40 per cent of this group developed venous thrombosis However preoperative thrombosis was not confined to either the patients receiving intravenous nutrition or to those with malignant disease

Venous thromboembolism is now recognized as one of the major hazards of operative treatment Some high risk patients may develop leg-vein thrombosis while in hospital prior to surgery despite remaining ambulant If deep vein thrombosis is established prior to operation prophylactic treatment instituted at the time of surgery is unlikely to prevent thromboembolism in these patients although it may limit extension of the clot Preoperative changes in coagulation factors possibly due to stress have been postulated and if important admission of patients to hospital immediately before surgery is unlikely to reduce the incidence of thromboembolism It would therefore appear that if the incidence of venous thromboembolism is to be further reduced prophylactic measures should be introduced on admission to hospital for high risk patients likely to spend more than a few days awaiting surgery

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Table I Retinal microaneurysms and immunoreactive insulin respond curve types in relationship to age and 5 year survival after myocardial infarction

MA vs IRI	*No*	*Mean age (x ± s)*	*Survivors 5 years (no)*	*Fatalities during 5 years (no)*	*Per cent mortality*
Positive–hyposecretion	4	63 ± 12	0	4	100
Positive–hypersecretion	7	5[illegible] ± 13	5	2	22
Positive–normosecretion	1	5[illegible]	1	0	–
Negative–hyposecretion	4	5[illegible] ± 8	0	4	100
Negative–hypersecretion	6	53 ± 11	5	1	17
Negative–normosecretion	1[illegible]	5[illegible] ± 12	12	5	30
Total	39	[illegible] ± 11	23	16	40

Abbreviations MA = microaneurysms IRI = immunoreactive insulin response curve

subjects presumably have asymptomatic or chemical diabetes

Three types of IRI response curves were observed normal hypersecretion with delayed peak, and hyposecretion (Fig 1) Sporadic microaneurysms in the macular region which represent an initial stage of microangiopathy were observed in 12 subjects, i e in ?5 per cent of the whole series (Fig ?)

We looked for correlations between the occurrence of microaneurysms impairment of glucose tolerance and IRI Among those 16 subjects with asymptomatic diabetes microaneurysms were found only in six This means that the defect in GTT is not a requirement for the microangiopathy A better correlation was observed with the IRI response curve (Table I) A normal IRI response was observed in only one of 12 subjects with microaneurysms. Four of them were hyposecretors and seven were hypersecretors with delayed peak Patients with impaired IRI were also observed among those without *microaneurysms* but relatively less frequently The latter tended to be younger We also observed a striking difference in the mortality rate over a 5 year period Hyposecretion of IRI seems to *carry a poor prognosis while the* prognosis for hypersecretors is obviously better

In conclusion it may be said that microaneurysms as an early sign of microangiopathy were a common finding in our series of patients after myocardial infarction even without overt diabetes mellitus The microvascular changes appeared to be more related to impairment of the IRI *secretion than to* an abnormal GTT The IRI response curve is of prognostic value for patients after myocardial infarction

Further studies are needed to evaluate the role of microangiopathy *in the development* of coronary atherosclerosis and the genesis of acute myocardial infarction More data are needed also on the occurrence of microangiopathy in systems other than the ocular fundus in such patients

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On artifacts in portable electrocardiographic monitoring

To the Editor

We read with interest the article by Krasnow and Bloomfield *in this* JOURNAL dealing with artifacts encountered during interpretation *of ECG*s obtained by Holter monitoring We appreciate the warning expressed by *the authors concerning* misinterpretations arising from technical errors Most of the described artifacts such as battery depletion (their Figs 1 2 and 11) broken lead (their *Fig 4) temporary* impairment of electrode *contact* (their Fig 8) are however obvious even according to the authors and can in our opinion be diagnosed easily by *any* trained technician and are *avoidable* by careful and proper operation of the system

While 14 out of the 15 examples presented as artifacts in the article deal with the technical faults resulting in a possible misdiagnosis of an arrhythmia or conduction disturbance

Letters to the Editor

Survival of valve replacement patients

To the Editor

In the article Clinical evaluation of aortic and mitral valve prostheses (AM HEART J 92 245 1976) Dr Burch and Dr Giles state that the survival rate of patients with aortic valve replacement may be slightly higher than that of patients with mitral prostheses [1] This is not substantiated by their next sentence nor by Fig 1 of the reference they cite The issue may be minor but the confusing contradiction perhaps warrants explanation

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REFERENCE

1 Duvoisin G E Wallace R B Ellis F H Jr Anderson M W and McGoon D C Late results of cardiac valve replacement Circulation 37 and 38 (Suppl II) 75 1968

Retinal microangiopathy in coronary heart disease without overt diabetes

To the Editor

Microangiopathy is supposed to be a characteristic but not specific complication of diabetes mellitus The cause of it is probably a defect of glycoregulation due to impaired insulin secretion About 40 to 45 per cent of patients with coronary heart disease without overt diabetes have an abnormal glucose tolerance test (GTT) and an elevated delayed peak in the immunoreactive insulin response curve (IRI) is a common finding [1] It is not entirely clear whether there exist interrelationships between microangiopathy and atherosclerosis of great vessels It has been suggested that they are linked pathogenetically microangiopathy of vasa vasorum impairing the vessel wall nutrition

The aim of this study was to establish whether abnormal glucose tolerance and immunoreactive insulin response tests often found in patients with coronary artery disease are commonly associated with microangiopathy and if such findings might have a prognostic value for the patient

The study population consisted of 37 men and two women (mean age 56 ± 11 years) with coronary artery disease They were studied 3 to 6 weeks after acute myocardial infarction diagnosed by WHO criteria Retinal angiography was performed by the method of Novotny and Alvis The GTT and IRI were assessed in the same time period The glucose load was 1 Gm /Kg (75 Gm maximum) and the standard orthotoluidin reaction was used for analysis IRI was estimated by the method of Hales and Randle using an insulin immunoassay kit (Amersham) All subjects were free of overt

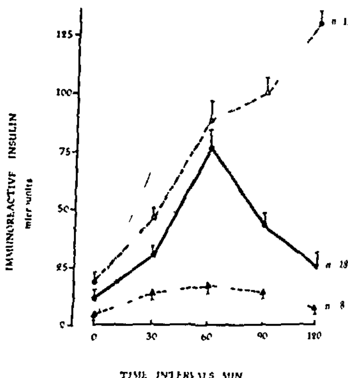


Fig 1 Types of immunoreactive response curves Mean values and S E M are given (vertical bars) Open circles = hypersecretion full circles = normosecretion triangles = hyposecretion The shaded area indicates normal IRI secretion as assessed in 15 non obese men with a normal coronary angiographic pattern



Fig 2 Retinal fluorescein angiography Microaneurysms appear in the macular region as white dots

diabetes and retinal microangiopathy was not visualized on routine opthalmoscopy or color photography of the ocular fundus

We found a blood sugar level of 120 mg per cent or higher two hours after the glucose load in 16 of 39 subjects These

event the recording is obtained on a previously used and unerased tape there is no chance of superimposed signals or the Siamese Twin" effect as described in the article

Our system also employs a tape cassette with safety features which prevents the problems of tape reversal which may lead to the diagnosis of a misleading Q Wave

Althou h artifacts related to electrode interfacing which are often easily recognizable will continue to exist in ours and other systems the artifacts of poor equipment performance no longer have to present a problem

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Reply

To the Editor

We wish to thank Drs Stern and Tzivoni and Dr Stein and Mr Peterson for their interest in our article and for their informative letters

The letter by Drs Stern and Tzivoni brings out some excellent points There is no doubt that the ST T changes recorded by Holter monitoring are not true artifacts They are electrical observations The main point we stress is that in our opinion the observation of ST T changes by Holter monitoring should be interpreted with caution Certainly Drs Stern and Tzivoni have proved that ST T changes may be associated with advanced coronary artery disease Our observation is that we have seen similar changes in patients in whom we believe the diagnosis of ischemic heart disease to be extremely unlikely We cannot prove this because further diagnostic tests were not done on the individuals. For the most part those individuals were monitored for symptoms other than those associated with coronary artery disease In other words Holter monitoring while a primary source for the identification of arrhythmias is probably a secondary source for the detection and evaluation of ischemic heart disease In the event ST T changes are observed by Holter monitoring confirmation by another diagnostic moiety should be sought in order to reduce the risk of overdiagnosis

We also believe that *The Editor* can attest to th fact that not all artifacts are obvious since during editorial review of the paper there was interobserver disagreement on the interpretation of what ultimately were the reported artifacts

The letter by Dr Stein shows that encouraging and welcome progress is being made to limit our ability to stumble

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their last so called artifact concerns the appearance of pseudo primary T wave change In this case the authors do not imply that these T wave changes are due to mechanical error of the system but attribute them to possible changes in body posture or position albeit admitting that proof is lacking for this assumption We certainly agree that postural T wave changes may be seen in some individuals when ECG is recorded (as a matter of fact by any method or system) in the supine and the orthostatic positions The appearance of T wave changes alone will not imply therefore underlying disease unless postural changes were excluded as is done routinely in all our patients prior to undergoing ambulatory ECG monitoring [3]

There is nothing novel in stating that the interpretation of the transient isolated T wave inversion is an unsolved problem whether observed during a bicycle or treadmill test right atrial pacing or ambulatory ECG monitoring While describing this alteration during everyday activities at rest or even during sleep [3] a reservation was always expressed as to their meaning It was therefore somewhat surprising to us to find advanced coronary pathology on arteriography in all seven patients who had this change on previous ambulatory ECG monitoring Evidently this small number of patients does not allow us to draw definite conclusions and further studies will be required to clarify the meaning of such transient isolated T wave inversions

In the Summary of their article Krasnow and Bloomfield state that changes in the ST segment may be misleading we could not find in their investigation any support for this statement Contrary to their belief (or disbelief) several authors [7] have recently expressed their opinion that ST segment alterations detected by ambulatory monitoring similar to ST depressions occurring on exercise testing are indicative of an underlying coronary disease and this method is therefore a valuable adjunct to other tests in detection of ischemic heart disease no doubt all these authors took it for granted that the method is used properly and all technical factors are dealt with meticulously

Finally we find the authors opinion that all anomalies detected by portable monitoring are artifactual until proved otherwise unfounded and not supported by the material presented in the article However we do find it important to stress the need for excellent care in all technical details of operating the system by well trained technicians and further critical evaluation of all findings by devoted and experienced physicians and in this respect ambulatory ECG monitoring is not different from other new and sophisticated tests we apply today in medicine

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More on artifacts

To the Editor

We read with interest the excellent article by Krasnow and Bloomfield entitled Artifacts in portable electrocardiographic monitoring which appeared in the March 1976 issue (AM HEART J 91 349 1976)

In our experience artifacts in long term ECG recordings may be categorized into two groups (1) artifacts related to the electrode and lead system and (2) artifacts related to the recording and playback instrumentation

Artifacts resulting from problems with electrode interfacing and patient movement may be considerably reduced by careful preparation of the skin by positioning of electrodes over cartilage bone and lean muscle mass by securely attaching the lead wires to the patient s chest and by proper shielding of patient cables Although electrode and lead artifacts may be reduced by these techniques they are not and may never be totally eliminated

Artifacts related to difficulties with instrumentation performance however are another matter Many of the problems of the Avionics equipment described by Krasnow and Bloomfield which may produce potentially serious misdirections of diagnosis and therapy are eliminated in newer systems Improved instrumentation presently exists which prevents the pseudo arrhythmias described in their article

Clinical Data has developed and uses recording and playback equipment designed to eliminate the problems resulting from battery and motor failure In our system we employ only disposable mercury cells Although these batteries would permit up to 40 hours of continuous recorder operation at constant voltage we use a fresh battery with each 24 hour recording This insures a constant motor speed (± 1 per cent) throughout the recording period and therefore pseudo sinus or pseudo atrial tachycardia cannot be produced

To further insure the control of tape speed which is essential to preventing pseudo supraventricular arrhythmias pseudo sinus arrest or pseudo sinus bradycardia a timing track derived from a crystal controlled oscillator is recorded directly onto a separate channel of the tape On playback this timing signal is fed through servo control circuitry and regulates the tape speed to compensate for any speed variations occurring on either recording or playback

The recording electronics for the data channel are frequency modulated (FM) and are compensated by the timing channel This not only insures a frequency response down to 0 05 Hz for proper ST segment evaluation but in the

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Editorial

The management of the patient with angina

David Short M D
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The scope for helping patients with angina has increased enormously over the past decade When I was an intern working at the National Heart Hospital in London in the 1950s it was by no means uncommon to see patients with the pale bloated features of myxoedema dragging themselves to hospital for a check up—half relieved of their angina but only half alive In the 1960s the beta blockers were introduced followed shortly by the operation of saphenous vein bypass Now the treatment of angina is well advanced and the great need is for the prevention of the underlying diseases particularly coronary atheroma

The basis of the management of a patient with angina is diagnosis in depth First of all angina must be recognized It is still often overlooked Attacks of pain or oppression occurring anywhere in the torso (though usually in the region of the upper or middle sternum) precipitated by effort or emotion and persisting for a few minutes must be regarded as anginal Radiation to one or both arms the throat lower jaw or back provides further confirmation of the diagnosis Difficulties arise when the pain is in an atypical site dependent on a combination of exercise with cold or a recent meal and induced by excitement rather than by effort and the electrocardiogram is normal even when recorded during strenuous effort

From th C d c Dep rtment Aberdee R y I I firmary Aberdeen Scotl nd

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Secondly it must be accepted that (malingering apart) a history of angina always indicates a reduced coronary reserve It has often been claimed that hiatus hernia and other disorders of the esophagus may produce an identical symptom but this has never been proved

Thirdly it must be realized that a reduced coronary reserve does not necessarily imply narrowing of the coronary arteries although that is by far the commonest cause In 7 to 10 per cent of cases angina may be due to other varieties of heart disease which cause either a reduction in coronary blood flow or an increase in myocardial work or both—for instance aortic valve disease hypertension and less commonly cardiomyopathy mitral stenosis or pulmonary hypertension Occasionally no evidence of heart disease (or any other disease) can be found

How often angina is due to non coronary disease cannot be stated precisely and no doubt varies from place to place In the postmortem series of Zoll and colleagues all the patients with angina whom they studied showed evidence of heart disease or hypertension Ninety per cent had coronary disease and the remaining 10 per cent were divided more or less equally between hypertension and valvar disease (aortic or mitral or both) In a recent clinical study[3] angina was due to aortic valve disease in approximately 3 per cent of the patients to hypertension in a further 3 per cent and to other forms of heart disease in 1 per cent Over a quarter of the patients with coronary disease had associated hypertensive disease and 3 per cent had associated severe aortic valve disease

Book reviews

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This is an excellent presentation of selected aspects of cardiovascular physiology This review includes discussions of blood viscosity the peripheral circulation control of plasma volume cardiopulmonary receptors the myocardium evolution of myocardial infarction and others The discussions are thorough though brief and the respective bibliographies to each chapter are extensive This book should not only interest physiologists and students but cardiologists who can appreciate the principles which apply in disease states they encounter in clinical practice This is a very good publication which is worth owning and which deserves careful study

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This is a rather extensive review of the mitral valve The book represents a publication of the discussions of a symposium held in Paris in May 1975 This reviewer is impressed with the extent of the discussion of one valve of the heart Some of those who entered in the discussions have not really conducted original or extensive investigations in the anatomy or function of the mitral valve Nevertheless some sections represent reviews of selected publications culled from the literature and should interest readers Surgeons will find the discussions of the influence of prosthetic valve type and size on the hemodynamic state at the mitral annulus to be interesting Most of the functional aspects of the normal valve are well known but the state of function in cardiac disease could have been emphasized more With the present interest in valve surgery echocardiography and mitral valve prolapse this book should be of interest As with most proceedings of symposia the discussions are most interesting and do reflect the opinions of the contributors and the gaps in knowledge concerning blood flow through the heart The contributors fail to indicate the level of accuracy or error or limitations in their measurement of cardiac output stroke volume blood pressure and other hemodynamic phenomena These limitations influence the extent to which data can be applied to the interpretation of hemodynamic phenomena

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These are the proceedings of an international symposium on central action of drugs used to regulate blood pressure The sessions of the symposium were divided into pharmacology and clinical pharmacology and therapeutics The papers are concerned with pharmacology and physiology of the neurogenic factors that influence and regulate arterial blood pressure and some of the commonly used drugs in clinical practice Clinicians should be interested in this book because of the importance of hypertension in the practice of medici e The book however is directed more to the intere ts of pharmacologists The discussions (questions and answers) are good This small book is important and does present new concepts as to the mechanisms of nerve function in response to vasoactive drugs This is a good book

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Editorial

The management of the patient with angina

David Short, M.D.
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The basis of the management of a patient with angina is diagnosis in depth. First of all angina must be recognized. It is still often overlooked. Attacks of pain or oppression occurring anywhere in the torso (though usually in the region of the upper or middle sternum) precipitated by effort or emotion and persisting for a few minutes must be regarded as anginal. Radiation to one or both arms, the throat, lower jaw, or back provides further confirmation of the diagnosis. Difficulties arise when the pain is in an atypical site, dependent on a combination of exercise with cold or a recent meal, and induced by excitement rather than by effort, and the electrocardiogram is normal even when recorded during strenuous effort.

Secondly, it must be accepted that (malingering apart) a history of angina always indicates a reduced coronary reserve. It has often been claimed that hiatus hernia and other disorders of the esophagus may produce an identical symptom, but this has never been proved.

Thirdly, it must be realized that a reduced coronary reserve does not necessarily imply narrowing of the coronary arteries, although that is by far the commonest cause. In 7 to 10 per cent of cases angina may be due to other varieties of heart disease which cause either a reduction in coronary blood flow or an increase in myocardial work, or both—for instance, aortic valve disease, hypertension, and, less commonly, cardiomyopathy, mitral stenosis, or pulmonary hypertension. Occasionally no evidence of heart disease (or any other disease) can be found.

How often angina is due to non coronary disease cannot be stated precisely and no doubt varies from place to place. In the postmortem series of Zoll and colleagues[2] all the patients with angina whom they studied showed evidence of heart disease or hypertension. Ninety per cent had coronary disease and the remaining 10 per cent were divided more or less equally between hypertension and valvar disease (aortic or mitral or both). In a recent clinical study, angina was due to aortic valve disease in approximately 3 per cent of the patients, to hypertension in a further 3 per cent, and to other forms of heart disease in 1 per cent. Over a quarter of the patients with coronary disease had associated hypertensive disease and 3 per cent had associated severe aortic valve disease.

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the onset of pain or oppression He should be advised to chew the tablet if the pain is severe and to discard it as soon as the symptom has been relieved He should also be advised until he is familiar with the effect of the tablet to sit down or recline after taking it in order to minimize the danger of fainting He should not be advised to lie flat because this increases the work of the heart and tends to prolong the attack It is also important to instruct the patient in the prophylactic use of the drug—that is to suck a tablet before starting any exertion which he knows from experience is likely to bring on his angina

Some patients find that glyceryl trinitrate in the standard dose of 0 5 mg causes such a headache that they prefer to put up with the angina Such patients should be advised that they are unusually sensitive to the preparation and need a smaller dose (0 3 mg) or alternatively that they should be advised to break the tablets and take half a tablet or less The trinitrate may be replaced by a less rapid and longer acting compound such as isosorbide dinitrate (sorbide nitrate) 5 to 20 mg three times a day Other patients find glyceryl trinitrate tablets helpful but are afraid of overusing them for fear they will lose their efficacy or lead to harmful side effects Such patients may be reassured on both accounts and told that as many as 20 tablets have been taken daily for long periods without harm

There has been some concern about the loss of potency of trinitrate tablets Earlier preparations using a cocoa base were somewhat unstable but the modern tablets in a mannitol base retain their activity for at least two years if stored in an air tight container protected from light and kept in a cool dry place Heat accelerates decomposition so that tablets kept close to the body might need to be changed rather sooner

The way glyceryl trinitrate works is still not absolutely certain It is undoubtedly a coronary vasodilator but the degree to which it can dilate segments of artery which are the seat of wide spread atherosclerotic narrowing is uncertain It usually causes a rapid fall in blood pressure which decreases the work of the heart It also dilates the peripheral veins with consequent pooling of blood in the hands and feet this reduces the venous return to the heart and hence its stroke output and work

Beta adrenergic blocking drugs Propranolol (Inderal) and oxprenolol (Trasicor) were a great advance in treating patients with severe angina Many new beta blocking drugs have appeared in the last two or three years but it is too early to say whether any of these is better than the well tried preparations Practolol (Eraldin) should no longer be used for treating chronic angina on account of its occasional serious side effects Not all patients are helped by beta blockade a few are actually made worse Nevertheless most patients improve and the results are often dramatic particularly in patients with tachycardia or other evidence of sympathetic overactivity In patients with associated hypertension beta blockade offers a chance of killing two birds with one stone

It is wise to start treatment with a small dose—for example propranolol 10 mg twice daily—and to double the dose every three or four days until relief is obtained or the heart rate falls below 60 beats/min If the angina remains unrelieved in spite of a reduction of heart rate below 60 beats/min a larger dose may still be successful but this should be done only with due caution Care should be taken in patients with a tendency to bronchospasm because this may be made worse If there is cardiac enlargement or abnormal ventricular function beta blockade should be accompanied by a diuretic but if the resting electrocardiogram is normal this precaution is unnecessary In a recent study it was shown that in patients on treatment with propranolol the addition of digoxin in a dose of 0 5 mg daily was followed by a striking improvement in exercise tolerance Since angina often subsides spontaneously particularly in the summer it may not be necessary to continue beta blockade indefinitely If the patient is getting no angina at all the dose should be gradually reduced and if the symptom does not return the drug may be stopped and kept in reserve

Other drugs With glyceryl trinitrate for the relief of the acute attack and beta blocking drugs for continuous prophylaxis the need for other drugs is greatly diminished Nevertheless there are patients who are not helped by beta blockade and for whose frequent attacks of angina glyceryl trinitrate produces only transient relief Many attempts have been made to find drugs with a more prolonged action than glyceryl trinitrate but with limited success Isosorbide dinitrate has

Fourthly it must be appreciated that even when angina is due basically to coronary arterial narrowing the symptom may be aggravated and the diagnosis complicated by extracardiac disease In the first place, there are diseases which decrease the oxygen content of the blood or increase the work of the heart—e g anemia and thyrotoxicosis Moreover certain diseases—such as chronic cholecystitis duodenal ulcer or cervical spondylosis may cause pain in the chest and aggravate and distort the pain of angina Anxiety smoking and obesity are other aggravating factors which need to be considered in treatment

To treat angina rationally it is necessary not only to make a comprehensive diagnosis but also to appreciate the prognosis of different patterns of angina Certain types of angina are particularly dangerous Crescendo angina—that is angina increasing in severity without any extracardiac cause such as anemia, increasing weight or a fall in atmospheric temperature carries a high incidence of myocardial infarction and death Angina which is unresponsive to adequate medical treatment also carries a serious prognosis Recent onset angina carries an increased risk [4] especially if the onset is sudden [1] On the other hand it is not sufficiently appreciated that in many patients angina subsides completely and may not return [4]

The question is often asked, Should every patient with angina be investigated by coronary arteriography? It can be argued that this is essential if the diagnosis is to be really comprehensive In some centers this is the policy and those who practice it claim that it provides information which is essential to rational treatment If the coronary arteries are normal the patient can be considerably reassured If there is severe left main stem narrowing many would consider the risk of medical treatment too high and advise operation While accepting the force of the argument in favor of universal investigation it is obviously not applicable worldwide because there are not the resources available, nor could the provision of such resources be justified In my view it is best, in most centers to concentrate on the investigation of those patients in the high risk categories of crescendo and medically intractable angina and perhaps those with recent abrupt onset

General principles of treatment

Any remediable factors such as hypertension severe aortic valve disease mitral stenosis anemia, thyrotoxicosis, as well as smoking and obesity, should be corrected Aggravating factors such as gallbladder disease and duodenal ulceration should be treated although operation should not as a rule be advised unless it is indicated on other grounds

Patients with angina should be advised to avoid activities which bring on the pain This usually means walking more slowly and avoiding exercise after a meal or in the coldest part of the day They should be specifically warned against lifting and pushing—for instance lifting heavy furniture or trying to push an automobile which has become stuck If they can avoid travelling to work in the rush hour they should do so It may be best to go earlier than usual when the parking is easier If the patient s occupation is strenuous and less heavy or demanding work is available a change should be advised but unsuitable work is far better than unemployment If the patient can move to a warm climate this is to be recommended There is some evidence to suggest that drugs such as the contraceptive pill and amitriptyline (Tryptizol) increase the risk of myocardial infarction and sudden death such drugs should therefore be avoided so far as possible

Nervous factors are very important in angina indeed Paul White went so far as to say that the nervous sensitivity of a patient was as important as all the pathological factors combined For this reason an optimistic reassuring attitude is important Indeed it is usually justified for the prognosis of angina is nothing like as bad as it is often thought to be Statements like You have a mild form of angina and Your heart is 95 per cent normal are often appropriate It is also important to avoid unnecessarily frequent review because frequent interrogation regarding symptoms tends to perpetuate them

Drug treatment

Glyceryl trinitrate Glyceryl trinitrate is still the mainstay of treatment and is usually sufficient in the mild case The patient should be instructed to carry his tablets with him constantly in a container with a tightly fitting cap (to avoid loss of potency by evaporation) He should be told to suck (not swallow) one of the tablets at

digoxin therapy in angina pectoris Ann Intern Med 83 449 1975

8 Barry W H Pfeiffer J F Lipton M J Tilkian A G Hultgren H N Effects of coronary artery by pass grafting on resting and exercise hemodynamics in patients with stable angina pectoris Am J Cardiol 37 8?3 19 6

9 Gunn G A and Mathur V S Surgical vs medical treatment for stable angina pectoris prospective randomized study with 1-4 year follow up European Congress of Cardiology Amsterdam 19 6

10 Kloster F E., Kremkau F L. Rahimtoola S H., Griswold H E Ritzmann L.W., and Starr A Prospective randomized study of coronary by pass surgery for chronic stable angina European Congress of Cardiology Amsterdam 19/6

11 National Co-operative Study Group to compare medical and surgical therapy in unstable angina pectoris I Report of protocol and patient population Am J Cardiol 37 896 19 6

been mentioned as a substitute for glyceryl trinitrate in patients who get a headache with the latter drug There are preparations which the makers claim can be chewed for relief of an attack or swallowed for prophylactic effect Delayed release trinitrin (Sustac) is sometimes helpful in patients with nocturnal angina A mild tranquilizer such as diazepam (Valium) may help an anxious or excitable patient over a particularly stressful period but stronger hypnotics have the disadvantage that they rarely abolish the attacks and often make the patient too confused to take his trinitrate properly In such cases a whisky nightcap is often effective Perhexiline maleate (Pexid) has sometimes been dramatically successful in relieving angina which has been resistant to other treatment including beta blockade Verapamil hydrochloride (Cordilox) and prenylamine (Synadrin) have also been reported effective in some patients The value of anticoagulant treatment and clofibrate (Atromid S) now appears to be negligible

Surgical treatment

The operation of saphenous vein bypass is a logical answer to what is in most cases basically a mechanical problem In experienced hands the operation carries a very low mortality rate and it is often dramatically successful in relieving severe *angina which has proved resistant to full medical* treatment including beta blockade In randomized control trials of medical versus surgical treatment ' the evidence strongly points to better cardiac function in patients treated surgically though the operation does not appear to alter the course of ischemic heart disease or to prolong life

Most patients with angina can live a more or less normal life with the help of glyceryl trinitrate and beta blocking drugs and a considerable proportion will lose their angina altogether Others will develop myocardial infarction or die suddenly whatever is done The only clear indication for saphenous vein bypass at present is angina which causes persistent disability after any remediable factors have been corrected and the medical armamentarium has been fully tried Such patients should be seriously considered for operation particularly if the electrocardiogram and x ray films show only slight myocardial damage

Treatment of recent onset and crescendo angina

Recent onset and crescendo angina often referred to as unstable angina, carry a high risk of myocardial infarction or sudden death If the angina appears only with effort, it is usually sufficient to insist on complete bodily and mental rest reinforced by sedation if necessary This often breaks the vicious circle, so that the patient may resume activity without the return of angina If the attacks come on at rest as well as with effort the situation is more dangerous and the patient should come under close observation in hospital Treatment with adequate doses of a beta blocker should be given as soon as possible unless there is bronchospasm or some other contraindication to the use of such drugs If anxiety is a factor, as it often is sedation is logical With such treatment the majority of patients come under control Anticoagulant therapy, either with heparin or warfarin has its advocates though it is by no means always successful in averting myocardial infarction Thrombolytic treatment, using strepokinase is currently being tried with some promising results Persistence of symptoms in spite of full medical treatment is an indication for urgent coronary arteriography with a view to coronary bypass surgery A prospective control trial is in progress to compare the results of medical and surgical treatment in unstable angina " Preliminary results indicate that the mortality rate is the same in both groups but long term relief of pain is better in the surgical group

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11 National Co operative Study Group to compare medical and surgical therapy in unstable angina pectoris I Report of protocol and patient population Am J Cardiol 37 896 1976

Clinical communications

The use of echocardiography in determination of reversible posterior wall asynergy

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Considerable recent attention has focused on the differentiation of reversible and irreversible asynergy utilizing the nitroglycerin ventriculogram.[1] Echocardiography has been found useful in detecting changes in global ventricular function induced by nitroglycerin in both normal patients and those with coronary artery disease. In a previous study echocardiographic determination of posterior wall asynergy was found to correlate well with the inferior wall ventriculographically. The present study was therefore undertaken to compare the echocardiographic and ventriculographic responses to sublingual nitroglycerin.

Methods

Nineteen patients had technically satisfactory echocardiographic tracings and cine ventriculography before and after nitroglycerin administration. Seventeen patients had coronary artery disease (≥75 per cent obstruction of one or more major coronary arteries) and two had cardiomyopathy (diffusely hypokinetic left ventricle with normal coronary arteries arteriographically). Ultrasonic evaluations were conducted 24 hours prior to cardiac catheterization with a Smith Kline ultrasonoscope (Ekoline 20A) employing a 2.25 mHz 5/8 inch diameter transducer focused at 10 cm. and coupled to a strip chart recorder (Irex). With the patient in a supine position, the transducer was placed in the fourth or fifth intercostal space near the left sternal border and directed posteromedially to obtain clear definition of the anterior mitral leaflet and septum. M mode scans of the left ventricle from the aortic root to the posterior papillary muscle were recorded by sweeping first superiorly and medially and then inferiorly and slightly laterally to record distinct echoes from the posterior mitral leaflet, left ventricular posterior wall, and posterior papillary muscle. Ventricular wall motion was assessed at a level in the sweep where the septal and posterior wall echoes were sharp and the mitral leaflets had become indistinct prior to the emergence of the posterior papillary muscle. This sector scan provides a view of the inferior wall between the mitral valve and the posterior papillary muscle.[4] A recent ventriculographic study has shown that this portion of the inferior wall is best viewed in the right anterior oblique projection.[5] Following recording of the control echocardiogram, nitroglycerin (1/150 gr. sublingual) was administered and the blood pressure and heart rate were monitored. When the systolic pressure decreased by 15 to 20 mm. Hg, the

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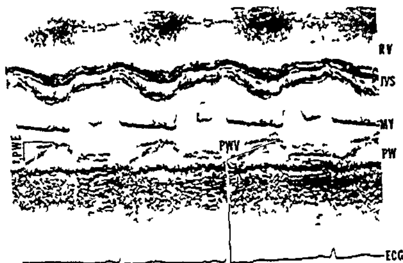


Fig 1 This figure illustrates normal posterior wall motion and the level in the sweep at which measurements were obtained Abbreviations *RV* = right ventricle *IVS* = interventricular septum *MV* = mitral valve *PW* = posterior wall *PWE* = posterior wall excursion *PWV* = mean posterior wall velocity *ECG* = electrocardiogram *PWE* = CD Abbreviations are consistent throughout all figures

echocardiogram was repeated as related above

The following parameters were obtained in all patients before and after administration of nitroglycerin The C-D amplitude of the systolic anterior motion of the endocardium was measured to obtain the posterior wall excursion (Fig 1) In addition mean posterior wall velocity was determined from the slope of a tangent line drawn from the endocardial surface at a point of 04 sec after the onset of the QRS to the peak systolic movement (Fig 1) as modified from the method of Kraunz and Kennedy

All 19 patients underwent cardiac catheterization in the postabsorptive state and were premedicated with 50 mg Demerol 50 mg Nembutal and 04 mg of atropine intramuscularly Right heart catheterization was performed via an antecubital vein and left heart catheterization either via a right brachial arteriotomy or percutaneously using the femoral artery Following the recording of the left ventricular pressure (using Statham P23Db transducers) and cardiac output (dye-dilution method using indocyanine green) left ventriculography was performed in the 30 degree right anterior oblique projection using 30 to 40 c c of meglumine diatrizoate (Renographin 76) When asynergy was observed *nitroglycerin* (1/150 gr sublingual) was administered 15 to 20 minutes following the initial ventriculogram so as to reduce the systolic pressure by 15 to 20 mm Hg After observation of the stability of the systolic pressure and heart rate for approximately 30 seconds the ventriculogram was repeated in the same degree of obliquity and using the same amount of contrast material and tube to tabletop distance Selective cine coronary arteriography was then performed using either the Sones or Judkins technique Hemodynamics were monitored and recorded on a Electronics for Medicine oscillographic recorder

Echocardiographic left ventricular posterior wall motion was qualitatively evaluated independently and blindly by two investigators (M M B M S F) and classified as normal or diminished These findings were then correlated with ventriculographic evaluations performed independently by two investigators (R H H V S B) Asynergy was classified as hypokinesis (decreased contraction) akinesis (absence of contraction) or dyskinesis (paradoxical systolic expansion) Quantitatively hemiaxis shortening of less than 25 per cent was considered hypokinetic and less than 5 per cent was considered akinetic Improvement following nitroglycerin was considered present when hemiaxis shortening increased by greater than 10 per cent Posterior wall motion on the echocardiogram was correlated with the inferior segment as seen on the right anterior oblique ventriculogram

Statistical analysis was performed using the Student s t test and all values are given as mean ± standard error of the mean (SEM)

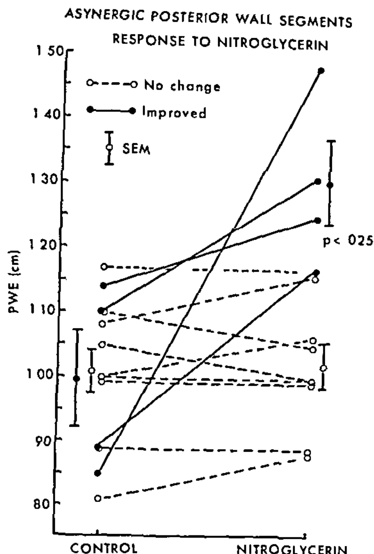


Fig 2 Effect of nitroglycerin on posterior wall excursion by echocardiography (See Results section) See *Fig 1* for abbreviations

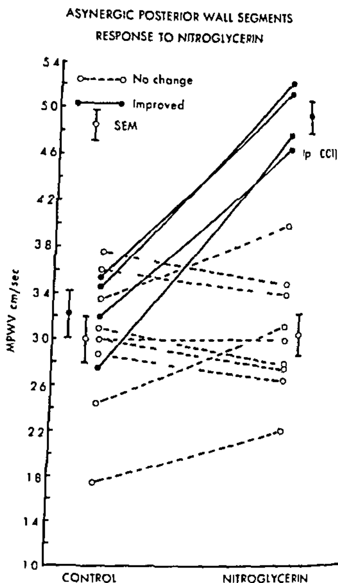


Fig 3 Effect of nitroglycerin on mean posterior wall velocity by echocardiography (See Results section) See *Fig 1* for abbreviations

Results

Thirteen of the 19 patients demonstrated abnormal posterior wall motion on echocardiography and ventriculography while six were normal by both techniques Of the 13 abnormal posterior wall segments four improved ventriculographically with an improvement in hemiaxis shortening from 12 0 ± 6 1 per cent to 29 0 ± 6 7 per cent (p < 02) In these four patients posterior wall excursion by echocardiography also increased from 0 99 ± 07 cm to 1 30 ± 07 cm (p < 025) after nitroglycerin (Fig 2) Mean posterior wall velocity also improved following nitroglycerin from 3 23 ± 17 to 4 95 ± 14 cm / sec (Fig 3) An example is illustrated in Fig 4

Nine posterior wall segments showed no change after nitroglycerin by ventriculography (hemiaxis shortening changed from 10 3 ± 5 7 to 6 5 ± 2 3 per cent) Corresponding echocardiographic posterior wall excursion was 1 01 ± 03 cm before and 1 02 ± 03 cm (Fig 2) after nitroglycerin administration Similarly posterior wall velocity was 2 99 ± 20 before and 3 05 ± 18 cm /sec after nitroglycerin (Fig 3) An example is illustrated in Fig 5 There was no significant difference in blood pressure response to nitroglycerin between the improved group (mean decrease in systolic pressure 21 3 ± 3 1 mm Hg) and the non responsive group (16 8 ± 2 4 mm Hg) The blood pressure response to nitroglycerin during catheterization was similar in both groups of patients

The six patients with normal posterior wall motion showed no significant change after nitroglycerin by echocardiography or ventriculography Ventriculographically, hemiaxis shortening

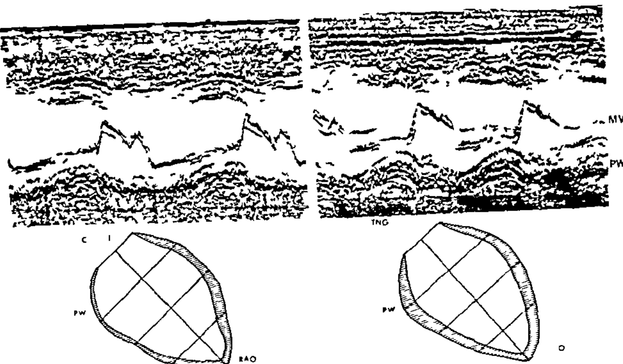


Fig 4 The control echocardiogram demonstrates markedly decreased posterior wall excursion (.88 cm) with corresponding ventriculographic evidence of inferior asynergy (hemiaxis shortening 7.0 per cent). Following administration of nitroglycerin posterior wall excursion increased significantly (1.18 cm) with improvement in ventriculographic hemiaxis shortening to 21 per cent. Abbreviations as in *Fig 1*.

changed from 36.3 ± 6.8 per cent to 44.3 ± 6.7 per cent. Following nitroglycerin there was no significant difference in posterior wall excursion (1.31 ± .06 cm before and 1.32 ± .11 cm after nitroglycerin) or mean posterior wall velocity (4.11 ± .52 before and 4.33 ± .56 cm/sec after nitroglycerin).

Discussion

Recently several studies have indicated that nitroglycerin ventriculography is a valuable means of differentiating reversible and irreversible asynergy. Ventriculographic evidence of improvement of an asynergic zone is presumptive evidence that the area contracts abnormally because it is chronically ischemic but not irreversibly scarred. A positive asynergic response to nitroglycerin correlates well with similar improvement following coronary bypass grafting to the artery subserving that zone.[1]

Studies from our laboratory and others have shown that single crystal echocardiography is capable of delineating the presence of posterior wall asynergy with considerable accuracy providing a noninvasive means of detecting asynergy in this area of the left ventricle without resorting to ventriculographic methods. The present study demonstrates that echocardiography correlates well with ventriculography in noninvasively determining the effect of nitroglycerin on posterior wall motion and its residual contractile ability. Thus all four patients who exhibited improvement of inferior wall asynergy ventriculographically demonstrated enhanced posterior wall motion by echocardiography (Figs 2, 3 and 4). Conversely of the nine patients showing *no* inferior wall improvement following nitroglycerin ventriculographically none demonstrated enhanced posterior wall motion by echocardiography (Figs 2, 3 *and* 5). Thus the echocardiogram is of particular value in detecting the presence, severity and potential reversibility of posterior asynergy. This is particularly useful in view of the difficulty of assessing this zone of the left ventricle by other noninvasive means.

Summary

Recent studies have indicated that nitroglycerin can delineate potentially reversible asynergic zones depicted ventriculographically. To assess the ability of the echocardiogram to detect reversible asynergy posterior wall motion was assessed

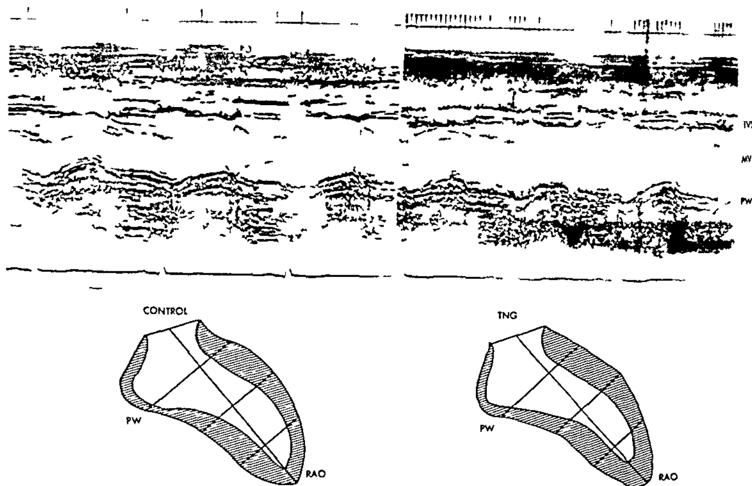


Fig 5 The control echocardiogram reveals decreased posterior wall excursion (.80 cm) with corresponding inferior wall asynergy (hemiaxis shortening 9 per cent). Following nitroglycerin administration posterior wall motion is unchanged with no improvement in hemiaxis shortening. Abbreviations as in *Fig 1*

in 19 patients both echocardiographically and ventriculographically before and after nitroglycerin. Thirteen of the 19 patients demonstrated abnormal posterior wall motion both by echocardiography and ventriculography while six were normal by both techniques. In 4 of the 13 asynergic areas posterior wall excursion improved following nitroglycerin (from 0.99 ± .07 to 1.30 ± .07 cm by echocardiography ($p < .025$) with a corresponding improvement in hemiaxis shortening from 12.0 ± 6.1 per cent to 29.0 ± 6.7 per cent ($p < .02$). In contrast, in nine patients in whom inferior segment hemiaxis shortening was unchanged following nitroglycerin, posterior wall excursion by echocardiography was similarly not improved (1.01 ± .03 cm before and 1.02 ± .03 cm after nitroglycerin). The effect of nitroglycerin on posterior wall velocity paralleled changes in posterior excursion. The six patients with initially normal posterior excursion showed no significant change by either echocardiography or ventriculography following nitroglycerin.

Thus, the echocardiogram is of considerable value in detecting both the presence and potential for improvement of asynergic posterior wall segments.

We wish to thank Ms Andrea Karkella, Marlene Fauerbach and Sandra Hicks for their technical assistance and Miss Regina Harrison and Mrs Linda Lightner for their secretarial assistance.

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Acute myocardial infarction and ischemic injury during surgery for coronary artery disease

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James F Pfeifer M D
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It is now well recognized that acute intraoperative myocardial infarction is a significant complication of coronary artery surgery Supporting evidence consists of the appearance of typical ECG signs of acute infarction in the immediate postoperative period accompanied by abnormal elevation of serum enzymes[1-3] In fatal cases autopsy studies have confirmed the diagnosis of acute infarction In addition many patients exhibit abnormalities in T waves and ST segments associated with abnormal enzyme elevations which probably represent lesser degrees of acute infarction with an intramural or subendocardial location The term acute ischemic injury has been applied to such occurrences[4]

It is the purpose of this study to determine the incidence of acute infarction and acute ischemic injury in the following four operative interventions for coronary artery disease

1 Internal mammary implants (Vineberg operation) for stable angina

2 Saphenous vein bypass for stable angina

3 Saphenous vein bypass grafts for unstable angina or the impending myocardial infarction syndrome

4 Saphenous vein bypass grafts performed in conjunction with valve replacement surgery or commissurotomy

The present study has the following features which permit a valid comparison between the four procedures

1 All operations were performed by the same operating team using similar techniques of cardiopulmonary bypass and vein bypass grafting

2 The group of patients studied did not have other surgical procedures performed, such as resection of ventricular aneurysms or endarterectomy

3 Selection of patients for internal mammary implants and vein bypass grafts was performed using a standard protocol which excluded patients with persisting evidence of left ventricular failure left ventricular aneurysm or other features associated with a high operative mortality

4 Pre and postoperative evaluation of the electrocardiograms and serum enzymes was carried out by a single group of observers using similar methods and criteria

For those reasons the present study should present a reasonably accurate comparative evaluation of the incidence of myocardial infarction and ischemic injury occurring in the four groups of patients evaluated

Materials and methods

Composition of study group

Internal mammary implants Forty patients were studied Criteria for selection for surgery was the presence of chronic, stable angina with a duration of at least one year Persisting symptoms despite medical therapy were present in all patients None had prior surgical procedures for the relief of angina Patients with severe hypertension chronic congestive failure or left ventricular aneurysm were excluded

Saphenous vein bypass grafts—Stable angina

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One hundred twelve patients Indications for surgery and exclusions were similar to those in the implant group above

Saphenous vein bypass grafts—Unstable angina Sixty eight patients Unstable angina was defined by the presence of at least one of the following criteria (1) Stable angina with a recent increase in severity (2) Angina of recent onset (3) Rest angina or acute coronary insufficiency of recent onset and (4) Angina with recent episodes of ventricular fibrillation or tachycardia Prior to surgery recent infarction was excluded by serial electrocardiograms and serum enzyme determinations

Combined bypass grafts and valve replacement surgery Seventy four patients All patients had significant valvular disease and obstructive coronary artery disease All had symptomatic valvular lesions of sufficient hemodynamic significance to warrant valve replacement In addition significant coronary disease was revealed by arteriography in all patients Obstructive lesions which decreased luminal diameter by > 50 per cent were considered significant

Diagnostic criteria Electrocardiograms were recorded on all patients prior to surgery and daily thereafter for seven days All tracings were reviewed independently by two observers using the following criteria for the diagnosis of acute myocardial infarction or acute ischemic injury which have been previously described

Infarction—Appearance of new persistent Q waves of 04 second duration or longer or new QS deflections associated with characteristic evolutionary changes in the ST segment and T waves The appearance of transient intraventricular conduction defects was not considered diagnostic of infarction unless new Q waves appeared True posterior infarction with a new R wave in V was not observed in any of the postoperative patients

Ischemic injury (1) Flat ST segment depression of greater than 2 mm in left ventricular leads lasting more than 48 hours (2) deep T wave inversions persisting for more than 48 hours (3) ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation and (4) absence of new significant Q waves or QS deflections

The following serum enzyme determinations were performed preoperatively and postoperatively on days 1 2 3 6 and 10 serum glutamic oxalacetic transaminase (SGOT) lactic dehydrogenase (LDH) and creatine phosphokinase (CPK) Upper limits prior to operation were considered to be 40 350 and 60 units respectively Standard analytical methods were employed

It is well known that cardiac and coronary surgery will result in an increase in serum enzymes during the immediate postoperative period in the absence of evidence of myocardial infarction or acute ischemic injury Previous studies from our hospital suggest that acceptable criteria for abnormal rises in serum enzymes in the immediate postoperative period consist of CPK values exceeding 200 units SGOT values exceeding 90 units and LDH values exceeding 900 units

These values may differ in other hospitals since they are dependent in part upon the surgical technique employed including the duration of cardiopulmonary bypass aortic cross clamp time and clinical status of the patients CPK values are not indicated in the tabular summaries since the cardiac fraction was not determined and the correlation of CPK elevations with ECG changes was poor

Results

Internal mammary implants A total of 40 consecutive patients were studied Thirty eight were males and two were females The mean age was 50 years (range 35 to 69 years) All had stable angina of at least six months duration None had persistent symptoms of left ventricular failure Thirty five had treadmill tests and 30 (86 per cent) were positive Twelve had right heart catheterization studies and none had a pulmonary artery wedge pressure exceeding 16 mm at rest Twenty six (65 per cent) had ECG evidence of prior myocardial infarction All had coronary arteriography Severe coronary artery disease involving at least two major vessels was present in all patients Surgery was performed from October 1965 to August 1971 The surgical technique employed has been previously described Twenty seven had single and 13 had double implants

ECG evidence of acute myocardial infarction was observed in the immediate postoperative period in 11 patients (27 5 per cent) and evidence of acute ischemic injury was observed in 12 patients (30 per cent)

Serum enzyme data are shown in Table I

Table I Number and incidence (%) of ECG abnormalities SGOT values over 90 units and LDH values over 900 units in 40 patients who had internal mammary implants for stable angina pectoris

	ECG abnormalities		*Abnormal enzymes*			
	No	*%*	*SGOT > 90*	*%*	*LDH > 900*	*%*
Acute infarction	11	27.5	5/8	62	7/8	88
Ischemic injury	12	30.0	4/9	44	4/10	40
Neither of above	17	42.0	0/14	0	0/12	0

Denominators indicate number of patients where enzymes were determined

Table II Number and incidence (%) of ECG abnormalities SGOT values over 90 units and LDH values over 900 units in 40 patients who had SVBG for stable angina

	ECG abnormalities		*Abnormal enzymes*			
	No	*%*	*SGOT > 90*	*%*	*LDH > 900*	*%*
Acute infarction	16	14.3	14/15	93	9/12	75
Ischemic injury	25	22.3	8/24	33	5/16	31
Neither of above	71	63.4	10/64	16	3/37	8

Denominators indicate number of patients where enzymes were determined

SGOT levels exceeded 90 units in 9 out of 31 patients (29 per cent) and LDH levels exceeded 900 units in 11 out of 30 patients (37 per cent)

If one examines abnormal elevations of either SGOT or LDH which were observed in 15 patients there were associated ECG signs of either acute infarction or ischemic injury in 11 patients (73 per cent)

The 30 day operative mortality rate in 40 patients was 10 per cent (four deaths) All four deaths were clearly due to intraoperative infarction with characteristic ECG changes in four patients and abnormal rises in SGOT and LDH in three patients One patient died 36 hours after surgery and no enzymes were obtained

Saphenous vein bypass grafts for stable angina A total of 112 consecutive patients with stable angina pectoris were studied All were males The mean age was 51 years (range 33 to 63 years) The clinical characteristics of these patients were similar to those in the internal mammary implant series since the criteria of selection for surgery was similar Forty one patients had multistage treadmill tests prior to surgery and 27 (66 per cent) had positive tests In 69 patients the mean ejection fraction was 62 per cent (range 89 to 22 per cent) The operative technique employed has been previously described None of the patients had procedures other than vein bypass grafts performed Single grafts were used in 33 patients double grafts in 59 and triple grafts were used in 20 The mean cardiopulmonary bypass time was 103 minutes (range 190 to 31 minutes), and the mean aortic cross clamp time was 17 minutes (range 46 to 5 minutes)

Results ECG evidence of acute myocardial infarction was found in 16 patients (14.3 per cent) and evidence of acute ischemic injury was found in 25 patients (22.3 per cent) Serum enzyme data are shown in Table II

Abnormal levels of SGOT were noted in 32 out of 103 patients (31 per cent) and abnormal LDH levels were present in 17 out of 65 patients (26 per cent)

In 38 patients who had an abnormal elevation of either SGOT or LDH there were 27 (71 per cent) who had ECG signs of acute infarction or ischemic injury

The 30 day operative mortality rate in 112 patients was 2.7 per cent (three deaths) In two patients death was clearly due to extensive myocardial infarction manifested by typical ECG changes and abnormal elevations of serum enzymes

Unstable angina A total of 68 patients was studied Sixty five were males and three were females The mean age was 54 years (range 35 to 72 years) All had unstable angina with a duration of acute symptoms of one to 180 days prior to hospital entry Four general clinical presentations were observed

1 Stable angina of more than 6 months duration with a recent increase in severity (70 per cent)

2 Acute coronary insufficiency or rest angina (23 per cent)

3 Recent onset of angina within 90 days of hospital entry (8 per cent)

4 Angina with episodes of ventricular tachycardia or ventricular fibrillation (5 per cent)

All 68 patients had acute transient electrocar

diographic changes during chest pain compatible with myocardial ischemia

None of the patients had clinical evidence of an acute myocardial infarction as evidenced by the appearance of diagnostic Q waves and evolutionary ST T wave changes or diagnostic serum enzyme elevations None of the patients had symptoms of persistent left ventricular failure Twenty eight (41 per cent) had ECG evidence of healed myocardial infarction All patients had coronary arteriography and severe coronary disease involving at least two major coronary vessels was present in all patients Forty four patients (65 per cent) had moderate abnormalities in left ventricular contraction and the mean ejection fraction determined in 31 patients was 69 per cent (range 90 to 33 per cent)

Surgery was performed between February 1971 and June 1975 All patients had saphenous vein bypass grafts without endarterectomy or other procedures The mean pump bypass time in 57 patients was 132 minutes (range 29 to 235 minutes) and the mean aortic cross clamp time in 42 patients was 30 minutes (range 5 to 75 minutes) Eleven had single grafts 36 had double grafts 19 had triple grafts and two had quadruple grafts

Results ECG evidence of acute myocardial infarction was observed in the immediate postoperative period in 14 patients (20 6 per cent) and evidence of acute ischemic injury was observed in 12 patients (17 6 per cent)

Serum enzyme data are shown in Table III

Abnormal levels of SGOT occurred in 27 of 66 patients (41 per cent) and LDH in 23 out of 64 patients (36 per cent) In 27 patients who had abnormal enzyme levels there were 20 (70 4 per cent) who had ECG signs of infarction or ischemic injury

The 30 day operative mortality rate in 68 patients was 1 5 per cent (one death) This death occurred in the operating room due to inability to maintain a suitable blood pressure after the operation No autopsy was obtained

Combined bypass grafts and valve replacement surgery A total of 74 consecutive patients were studied The mean age was 59 years (range 43 to 81 years) Seventy patients were males and four were females The primary indication for surgery was valvular heart disease and vein bypass graft surgery was performed because of the presence of significant obstructive lesions of major coronary arteries demonstrated by selective coronary arteriography In all patients symptoms were primarily related to valvular heart disease

The operations performed are summarized in Table IV Forty three patients had single vein bypass grafts 27 had double grafts and four had a triple graft Mean bypass time was 142 minutes (range 51 to 270 minutes) Mean aortic cross clamp time in 64 patients was 47 minutes (range 0 to 90 minutes)

Table III Number and incidence (5) of ECG abnormalities SGOT values over 90 units and LDH values over 900 units in 40 patients who had SVBG for unstable angina

	ECG abnormalities		*Abnormal enzymes*			
	No	*%*	*SGOT > 90*	*%*	*LDH > 900*	*%*
Acute infarction	14	20 6	13/14	93	12/14	86
Ischemic injury	12	17 6	7/12	58	5/12	42
Neither of above	42	62	7/40	17.5	6/38	16

Denominators indicate number of patients where enzymes were determined

Table IV Valve replacement and valvular surgery performed in 74 patients who also had SVBG surgery The 9 other operations included 5 patients who had mitral commissurotomy and 4 who had mitral annuloplasty

	No
Aortic valve replacement	50
Mitral valve replacement	11
Mitral and aortic valve replacement	4
Other valve operations	9

Table V Number and incidence (%) of ECG abnormalities SGOT values over 90 units and LDH values over 900 units in 40 patients who had valve replacement surgery and SVBG surgery

	ECG abnormalities		*Abnormal enzymes*			
	No	*%*	*SGOT > 90*	*%*	*LDH > 900*	*%*
Acute infarction	15	20	12/14	86	10/13	77
Ischemic injury	28	38	24/28	86	20/23	87
Neither of above	31	42	9/28	32	7/22	32

Denominators indicate number of patients where enzymes were determined

Table VI Incidence of SGOT levels exceeding 90 units and LDH units exceeding 900 units in patients with ECG evidence of acute infarction *ischemic injury or neither of these ECG abnormalities The analysis includes all patients with abnormal elevations of SGOT or LDH*

ECG changes	*SGOT elevated (%)*	*LDH elevated (%)*
Acute infarction	79	68
Ischemic injury	56	44
Neither of above	16	10

Table VII Incidence of acute myocardial infarction (AMI), acute ischemic injury (AII) abnormal SGOT elevations and abnormal LDH elevations in the four groups of operations evaluated

	No	*AMI (%)*	*AII (%)*	*SGOT↑ (%)*	*LDH↑ (%)*
Vineberg	40	27 5	30 0	29	37
SVBG–Stable AP	112	14 3	22 3	31	26
SVBG–Unstable AP	60	20 8	17 6	41	36
VR + SVBG	74	20 0	38 0	64	64
VR only	126	7 0	30 0	32	37

Data from valve replacement operations also was obtained from a previous study

The operative technique employed in the valve replacement operation has been previously described

Results ECG evidence of acute intraoperative myocardial infarction was found in 15 of 74 patients (20 per cent) and evidence of acute ischemic injury was noted in 28 patients (38 per cent)

Serum enzyme data are shown in *Table V*

SGOT levels exceeded 90 units in 45 patients (64 per cent) and LDH exceeded 900 units in 37 patients (64 per cent)

In 53 patients who had an abnormal elevation of either SGOT or LDH there were 43 patients (81 per cent) who had ECG signs of acute infarction or ischemic injury

Nine operative deaths (in 30 days) occurred for a mortality rate of 12 2 per cent Four deaths occurred in association with ECG and serum enzyme evidence of acute intraoperative myocardial infarction

Discussion

Most previous reports of intraoperative myocardial infarction during coronary surgery have only identified patients who had the appearance of ECG abnormalities compatible with acute transmural myocardial infarction In this study and in previous studies from this hospital an additional group of patients have been identified who have had ECG evidence of acute ischemic myocardial injury[1] Electrocardiographic abnormalities in this group have consisted of changes in the T waves and ST segments compatible with severe ischemia or injury and in some patients *recurring episodes of ventricular tachycardia or* AV block Such changes occurring in the presence of abnormal elevations of serum enzymes strongly suggest that subendocardial intramural or focal infarction is probably present Table VI *illustrates the incidence of abnormal serum* enzymes in all patients with ECG changes of acute transmural infarction ischemic injury patterns and neither of these ECG changes in the *immediate postoperative period* In patients *without such ECG changes abnormal rises of* either SGOT or LDH were observed in only 16 per cent and 10 per cent respectively In patients with ischemic injury patterns abnormal rises of SGOT or LDH occurred in 56 per cent and 44 per cent respectively *These data should be compared with patients with typical ECG signs of* transmural infarction where the incidence of abnormal SGOT and LDH levels were 79 per cent and 68 per cent respectively These data support the validity of *identifying acute ischemic injury* as a complication of coronary surgery and indicate that in approximately 50 per cent of such episodes acute myocardial infarction is probably present based on the presence of associated eleva*tions in serum enzymes and ECG abnormalities* It would appear therefore that the true incidence of acute myocardial infarction associated with coronary surgery is probably higher than is *generally reported*

Support for this view can be obtained by inspection of Table VII and Fig 1 In each operation the incidence of abnormal enzyme elevations *is greater than the incidence of acute* myocardial infarction and in three operations (*vein bypass grafts for stable angina for unstable angina and vein bypass grafts and valve replace*ment surgery) the incidence of abnormal enzyme

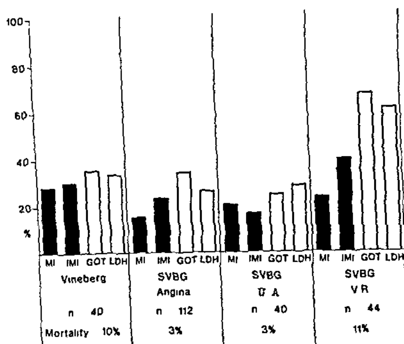


Fig 1 Comparative incidence of myocardial infarction (*MI*) ischemic myocardial injury (*IMI*) and abnormal elevations of SGOT (*GOT*) and *LDH* in four operations for coronary artery disease *SVBG* = saphenous vein bypass graft *UA* = unstable angina *VR* = valve replacement Operative mortality indicated at the bottom of panels

elevations is almost equal to the sum of the acute infarcts and acute ischemic injury episodes

Serum enzyme data in the present study have several limitations Isoenzymes (myocardial components) for CPK and LDH were not determined Total CPK values are unreliable and do not correlate well with ECG changes probably due to the effect of skeletal muscle CPK LDH values may be high due to hemolysis in addition to myocardial infarction SGOT values are probably most reliable since very few patients with right ventricular failure and hepatic congestion or necrosis were subjected to surgery Such patients were confined to the group of patients having combined valve replacement surgery and vein bypass grafts Only 4 out of 74 of these patients had right ventricular failure prior to surgery and preoperative serum enzymes were normal in these patients

It is evident from Fig 1 that the highest incidence of acute infarction was observed in patients who had internal mammary implants Several reasons may account for the high incidence of these complications observed with internal mammary implants The patients represent the early initial experience with the operation hence the surgical technique may not be optimum Internal mammary implantation does not provide the immediate revascularization that can be accomplished with vein bypass graft surgery The internal mammary implant operation causes considerably more epicardial and myocardial damage in the creation of the myocardial tunnel than does the vein bypass graft technique

The high incidence of enzyme elevations in the group of patients having combined valve replacement surgery and vein bypass grafts is probably due in part to the longer aortic cross clamp time required for the combined procedure[6] It has been previously shown that valve replacement surgery alone even in the absence of significant coronary artery disease may be accompanied by acute infarction ischemic injury or abnormal rises in serum enzymes These complications tended to occur more frequently in patients with double valve replacement operations and with prolonged cross clamp times These data are summarized in Table VIII The incidence of perioperative infarcts and acute ischemic injury is not significantly higher than in operations for stable and unstable angina This may be due to the difficulty

Table VIII Cardiopulmonary bypass time and aortic cross clamp time in patients with valve replacement and SVBG survey (VR & SVBG) valve replacement alone (VR) SVBG for stable angina and SVBG for unstable angina

	Bypass time (minutes)	*Cross clamp time (minutes)*
VR & SVBG	142	47
VR alone	88	43
SVBG Stable angina	103	17
SVBG Unstable angina	132	30

This group had more grafts per patient than the group with stable angina i e 2 2 grafts per patient compared to 1 9 grafts

Table IX Mean of highest enzyme values observed in four operations in patients with ECG signs of acute infarction or acute ischemic injury

Operation	*SGOT* *Acute infarcts*	*SGOT* *Ischemic injury*	*LDH* *Acute infarcts*	*LDH* *Ischemic injury*
Vineberg	167	153	1305	1219
SVBG–Unstable AP	217	170	1054	894
SVBG–Stable AP	194	94	1434	810
SVBG + VR	384	185	1806	1270

in the ECG diagnosis of infarction in this group of patients, most of whom had abnormal preoperative ECGs including left ventricular hypertrophy and bundle branch block patterns

In the group of patients having valve replacement surgery and bypass grafts 30 patients who had acute infarction or ischemic injury with abnormal enzymes had a mean bypass time of 158 minutes and a mean cross clamp time of 50 minutes compared to 118 minutes and 42 minutes respectively in 20 patients without these complications A more detailed analysis revealed that all patients (combined aortic valve replacement and vein bypass graft) with cross clamp times exceeding 70 minutes and 88 per cent of patients with anoxia plus fibrillation times exceeding two hours developed myocardial infarcts

Most of the data presented in this study relate to the *incidence* of intraoperative infarction and acute ischemic injury in the four types of operations The amount of myocardial necrosis occurring with such episodes can be roughly related to the magnitude of the enzyme elevation associated with the ECG changes These data are indicated in Table IX It is evident that the highest mean levels of enzymes were observed in patients who had combined vein bypass grafts and valvular surgery This difference is at a significant level (P = < 012) The highest *incidence* of serum enzyme abnormalities in this operation probably indicates a greater amount of myocardial necrosis Patients with left ventricular hypertrophy are especially susceptible to myocardial injury with prolonged ischemic arrest and cross clamp times

Acute intraoperative myocardial infarction is not only an important non fatal complication of coronary surgery but is also an important cause of death since 10 of the 17 deaths occurring in the combined series of 294 patients were associated with clear evidence of recent myocardial infarction Similar observations have been reported by Assad Morell and co workers [11] In 500 consecutive patients undergoing saphenous vein bypass surgery perioperative infarction occurred in 67 (13 per cent) and 10 of the 16 deaths were due to infarction [11]

Summary

The incidence of myocardial infarction acute ischemic injury and associated serum enzyme abnormalities has been evaluated in four operations involving the coronary circulation The highest incidence of infarction was associated with internal mammary implantation (Vineberg procedure) There was no significant difference in the incidence of infarction ischemic injury or abnormal enzyme levels between patients with stable angina and those with unstable angina who had vein bypass surgery In operations involving combined vein bypass grafting and valve replacement surgery the incidence of abnormal serum enzyme elevations was higher than in any other procedure The incidence of infarction and acute ischemic injury in combined operations was similar to that in other procedures but this may have been due to the difficulty in the ECG diagnosis of infarction in this group of patients most of whom had abnormal preoperative ECGs

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Postmortem diagnosis of ventricular fibrillation by K and Na distribution in the myocardium and skeletal muscle in out-of-hospital sudden death from acute ischemic heart disease

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Epidemiologic studies have shown that out-of-hospital death makes up 75 per cent of the total mortality from acute ischemic heart disease.[1-3]

Experimental data[4] and some clinical observations[5-8] suggest that the main cause of out-of-hospital death is ventricular fibrillation. However, there is no exact data on the percentage of sudden death from ventricular fibrillation in total mortality from acute ischemic heart disease. It is accounted for by the fact that in the majority of cases ventricular fibrillation is diagnosed neither in the patient's lifetime, as it usually occurs in the absence of medical care, nor in postmortem examination, since routine histologic study does not reveal any significant changes.[9-11] The application of histochemical, electronmicroscopic, and other methods such as fluorescent and radioisotope scanning of the heart have also proved ineffective for the recognition of these changes. The latter either do not develop rapidly enough or are masked by a postmortem autolysis.

Meanwhile, the knowledge of the frequency of ventricular fibrillation as a complication of acute ischemic heart disease is necessary for the evaluation of preventive treatment.

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For these reasons we decided to work out a method for a postmortem diagnosis of ventricular fibrillation in cases of out-of-hospital sudden death from acute ischemic heart disease.

Five main complications may cause death from acute ischemic heart disease both in and out of hospital: (1) ventricular fibrillation, (2) heart rupture, (3) thromboembolism, (4) heart failure, and (5) cardiogenic shock.

So, for the postmortem diagnosis, ventricular fibrillation is to be differentiated from four other causes of death. Two of them—heart rupture and thromboembolism—can be established at autopsy. As for heart failure, cardiogenic shock, and ventricular fibrillation, the routine postmortem examination cannot reveal any specific changes to differentiate one from another. Ventricular fibrillation differs from heart failure and cardiogenic shock in the duration of dying. The death from ventricular fibrillation is instantaneous and the death from heart failure and cardiogenic shock is non-instantaneous with an agonal period. We supposed that postmortem establishment of the duration of dying might have been used for the diagnosis of ventricular fibrillation and the duration of dying might have been determined by K and Na distribution in the myocardium and skeletal muscle.

K and Na distribution in the heart and skeletal muscle was first used for the postmortem diagnosis of local myocardial ischemia in the case of sudden death by Chait.[12-14] On Raiskina's suggestion this method was recommended for further

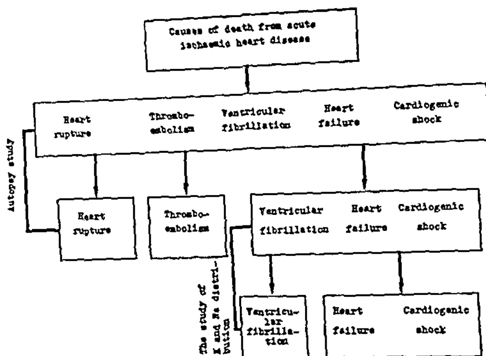


Fig 1 Schematic representation of the method of postmortem diagnosis of ventricular fibrillation

studies at the conference on pathological diagnosis of acute ischemic heart disease in Geneva in 1969 and was successfully used in later studies [11]

We supposed that K and Na distribution in the heart might not only have shown the existence of the ischemic area in the heart but also the type of death—i e instantaneous or non instantaneous We believed that the changes in K distribution in the heart and skeletal muscle could be determined only if hypoxic efflux of K from the cell took place in the patient s lifetime while blood flow was maintained Then on coming out of the cell K is washed away with the blood and its tissue content is decreased If K efflux takes place postmortem when blood flow is stopped then K remains in the extracellular medium and its total content in tissue does not change

Hence the area in which hypoxia occurred in the patient s lifetime will be characterized by the reduction of K content irrespective of the kind of death K content in non ischemic parts of the heart and skeletal muscle will depend upon the length of time it took the patient to die in the case of instantaneous death when hypoxia in these tissues is only postmortem K content will be normal and in the case of non instantaneous death when hypoxia already exists in the patient s lifetime during the agonal period K content in them will be reduced In all cases the changes in Na content must be oppositely directed

If this supposition is right then in the case of ventricular fibrillation K content must be reduced and Na content must be increased only in a limited area in the case of cardiogenic shock and heart failure these changes must occur not only in a limited area but in the whole heart and also in the skeletal muscle

The purpose of this study was to find out differences in K and Na distribution in the heart and skeletal muscle depending on the length of time it took the patient to die and to use these differences for the postmortem diagnosis of ventricular fibrillation in case of sudden death from acute ischemic heart disease

Methods

1 Study of the dependence of K and Na distribution in the heart and skeletal muscle on the duration of dying This dependence was studied in the city of Krasnoyarsk for a period of three years

In order to discover differences in K and Na distribution in connection with the length of time it took the patient to die K and Na concentration

Table I K and Na distribution in the heart and skeletal muscle in case of instantaneous and non instaneous coronary and non coronary death (mean data)

Kind of death	Number of cases	Left ventricle				Ventricular septum	
		K		Na	K/Na	K	
		mg%	%	mg%		mg%	%
I Coronary instantaneous	34	147 ± 5 3	56	139 ± 2 5	1 1 ± 0 05	156 ± 6	5
II Coronary non instantaneous	11	125 ± 5	48	139 ± 3 7	0 8	13, ± 7 3	50
III Non coronary instantaneous	10	262 ± 1 6	100	119 ± 2 8	2 2 ± 0 05	272 ± 9 5	100
IV Non coronary non instantaneous	12	168 + 3	64	132 ± 5	1 2	136 ± 11	50
p I III		0 001	0 001			0 001	0 01
p II IV		0 001	0 25			0 5	0 5
p III IV		0 001	0 05			0 001	0 0'
p I II		0 001	0 5			0 001	0 5

in the heart and abdominal rectal muscle was assessed in 67 deceased patients and these were subdivided into four groups

The first group consisted of 34 patients who died out of hospital The study of the circumstances of death carried out by the ambulance physician showed that the death was instantaneous with symptoms of acute coronary insufficiency

The second group consisted of 11 patients who died in hospital with the diagnosis of myocardial infarction complicated with cardiogenic shock where the agonal period lasted several hours

The third group was a control to the first one it consisted of 10 persons who died instantaneously of non coronary injures skull fracture knife or bullet wound of the head

The fourth group was a control to the second one it consisted of 12 men who died with an agonal period of non coronary diseases

The determination of K and Na was performed by flame photometer Burck s method in Chait s modification[1] [4] was applied Nine to ten samples weighing 150 to 250 mg were taken from the left and right ventricles septum and abdominal rectal muscle It proved to be sufficient to detect the heterogeneity in K and Na distribution in different parts of the heart and in the skeletal muscle

2 Postmortem establishment of ventricular fibrillation in the case of sudden death The heterogeneity in K and Na distribution in various parts of the heart and in the skeletal muscle enables us to detect the presence of local myocardial ischemia and to establish the length of time it took the patient to die

If K and Na distribution in the heart and skeletal muscle indicates that there is an area of ischemia in the heart and the death was instantaneous then to diagnose ventricular fibrillation two other causes of instantaneous death—heart rupture and thromboembolism must be excluded at autopsy

The method of diagnosis of ventricular fibrillation in cases of sudden death is schematically represented in Fig 1 Main causes of sudden death from acute ischemic heart disease can be heart failure cardiogenic shock thromboembolism heart rupture and ventricular fibrillation

Autopsy findings give an opportunity to exclude the cases of heart rupture thromboembolism and strongly pronounced cardiac insufficiency The other cases make up a mixed group in which the causes of sudden coronary death may be cardiogenic shock less pronounced cardiac insufficiency and ventricular fibrillation

The study of K and Na distribution in the heart enables us to differentiate cardiogenic shock and heart failure from ventricular fibrillation

Results

1 K and Na content in the heart and skeletal muscle in case of instantaneous and non instantaneous coronary and non coronary death The

Ventricular septum		*Right ventricle*				*Skeletal muscle*			
Na		*K*		*Na*		*K*		*Na*	
mg%	*K/Na*	*mg%*	*%*	*mg%*	*K/Na*	*mg%*	*%*	*mg%*	*K/Na*
134 ± 2 3	1? ± 0 05	156 ± 3 1	86	140 ± ? ?	1 1 ± 0 17	235 ± 2 6	91	8? ± 0 86	2 8
133 ± 3 6	1 01	140 ± 2 3	77	134 ± 6 2	1 1	1?2 ± 4 8	66	90 ± 5 3	1 9
1?0 ± 1 3	2 ± 0 15	181 ± 4	100	136 ± 3 1	1 2 ± 0 1	259 ± 4 9	100	81 ± 1 6	3
127 ± ?	1	148 ± 5	72	130 ± 3	1 1	186 ± 6	?0	96 ± 2 1	2
		0 00?	0 5			0 00?	0 5		
		0 5	0 1			0 001	0 ?5		
		0 001	0 001			0 001	0 001		
		0 001	0 001			0 001	0 2		

data obtained is represented in Table I According to the table the changes in K content were considerable while the changes in Na content were less pronounced K and Na content in cases of instantaneous non coronary death (group III) served as a control and in other cases concentration of K and Na was expressed in a percentage of the control values

The dependence of K and Na distribution in the myocardium and skeletal muscle on the presence of coronary changes is seen in comparing groups I and III and II and IV

It was discovered that K *content in the left* ventricle and ventricular septum in the case of sudden coronary death (Group I) is reduced respectively to 56 per cent and 57 per cent of control values being lowered insignificantly in the right ventricle and the skeletal muscle respectively to 86 per cent and 91 per cent Thus there is definite heterogeneity in K content of the heart in the case of instantaneous coronary death

In the case of non instantaneous coronary death (Group II) K content in the left ventricle and ventricular septum is lowered sharply to 48 per cent and 50 per cent but it is lowered also in the right ventricle and skeletal muscle to 77 per cent and 66 per cent Thus in case of non instantaneous coronary death the heterogeneity *in* K content in the myocardium is less pronounced than in instantaneous coronary death (Group I) but it is still more marked than in *non instantaneous* non coronary death (Group IV)

The dependence of K and Na distribution in the myocardium and skeletal muscle *on the* length of time it took the patient to die is clearly seen in comparing Groups I and II and III and IV (which differ only in the length *of time it took the* patient to die)

The difference between instantaneous and non instantaneous non coronary death is that in the former (Group III) *the total content of K does* not change in all parts of the heart and in the latter *(Group IV)* it is lowered but there is no clear heterogeneity between various parts of the heart and skeletal muscle

The differences in K content in the case of instantaneous and non instantaneous coronary death are of major interest K content in the left *ventricle* and ventricular septum is lowered *almost to the* same degree both in case of instantaneous (Group I) and non instantaneous (Group II) *death* but in the right ventricle and skeletal muscle *the differences* are considerable—a slight decrease in the case of instantaneous death and a sharp decrease in the case of non instantaneous death

Each kind of death is best characterized by *the* interrelation of K and K/Na ratio between the left ventricle and skeletal muscle (Fig 2)

If K content and K/Na ratio in *the left* ventricle and the skeletal muscle is near control values it indicates *instantaneous non coronary death*

If K content and K/Na ratio is lowered both in

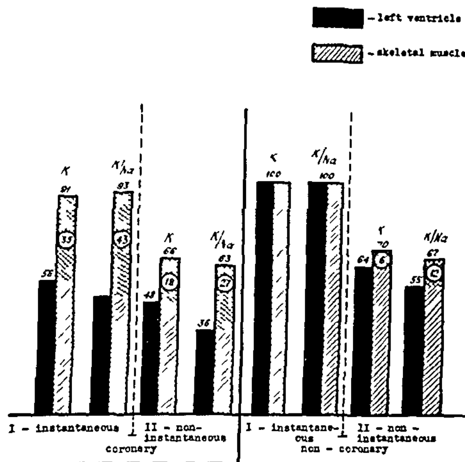


Fig 2 K content and K/Na ratio in the left ventricle and skeletal muscle in case of instantaneous and non instantaneous coronary and non coronary death (In percentages compared to instantaneous non coronary death)

the left ventricle and skeletal muscle and the difference between them is small it indicates *non instantaneous non coronary death*

If K content and K/Na ratio in the left ventricle is sharply decreased and in the skeletal muscle it is close to the control values and the differences between them are great it indicates *instantaneous coronary death*

If a sharp decrease in K content and K/Na ratio is combined with the decrease in the skeletal muscle and thus the differences between them are not very great it indicates *non instantaneous coronary death*

Thus two main signs are essential for the determination of the kind of death (1) the existence of significant differences in K content and K/Na ratio between the left ventricle and the skeletal muscle is the sign of coronary death and the absence of them is the sign of non coronary death, (2) the existence of significant decrease in K content and K/Na ratio in the skeletal muscle is the sign of non instantaneous death and the absence of it is the sign of instantaneous death

2 Postmortem determination of the frequency of ventricular fibrillation in case of sudden death The three year study in Krasnoyarsk (1968 1970) shows that out of 1 515 patients with acute ischemic heart disease 671 patients died, 508 of them dying suddenly out of hospital and 163 dying in hospital

A study of the circumstances of death by questioning witnesses of the death by autopsy studies and postmortem determination of K and Na distribution in the heart and skeletal muscle in a selective group allowed us to calculate the frequency of sudden death from ventricular fibrillation among the cases of out of hospital death and to compare it with the frequency of sudden death in hospital (Table II)

The data obtained show that only 6% of all cases of ventricular fibrillation take place in hospital and the other 94% take place out of hospital No wonder that ventricular fibrillation leads to the death of only 14 7% of hospital patients with acute ischemic heart disease while cardiac insufficiency and cardiogenic shock[19, 20] remain the major causes of hospital death

Not too long ago this distribution of the causes of death from acute ischemic heart disease in hospital was ascribed to the total mortality from

Table II Frequency of sudden death from ventricular fibrillation in hospital and out of hospital patients in Krasnoyarsk (1968 1970)

	Died of ischemic heart disease		*Died of ventricular fibrillation*		*The percentage of ventricular fibrillation in*	
	Number of patients	%	*Number of patients*	%	*Suffering acute ischemic heart disease (1515)*	*Died of acute ischemic heart disease (671)*
Out-of hospital	508	75 7	373	94 0	24 5	73 7
In hospital	163	24 3	24	6 0	1 6	14 7
Total	671	100	397	100	26 2	59 1

it But hospital mortality makes up only 24 3 per cent of total mortality while out of hospital death which is as a rule sudden makes up 75 7 per cent of the total mortality rate

If we regarded only instantaneous death then ventricular fibrillation would be almost the only cause of it But taking into account that the death is considered sudden if it occurs within six hours of the onset of the first symptoms the percentage of ventricular fibrillation is lower and constitutes 73 7 per cent of all cases of out of hospital sudden death and 59 1 per cent of the total number of patients dying from acute ischemic heart disease If we compare the number of ventricular fibrillation cases to the general number of patients with acute ischemic heart disease then ventricular fibrillation in hospital makes up only 1 6 per cent out of hospital makes up 24 5 per cent and the total number of ventricular fibrillation cases constitutes 26 2 per cent of patients with acute ischemic heart disease

As is apparent from the data above every fourth patient with acute ischemic heart disease is under the threat of dying of ventricular fibrillation and almost two thirds of the deaths from acute ischemic heart disease are due to ventricular fibrillation

Discussion

The dependence of K and Na distribution in the heart and the skeletal muscle upon the length of time it takes the patient to die as discovered in this work and the dependence of the distribution of these ions on the presence of local myocardial ischemia as found earlier may be explained as follows

It is generally known that under hypoxic conditions intracellular K in the heart and skeletal muscle comes out into extracellular medium and while blood flow is maintained it is washed out with the blood If hypoxia occurs postmortem after cessation of blood flow then on leaving the cell K is not washed out with the blood and remains in the extracellular medium

This is how we can determine if hypoxia occurred postmortem or in the patient s lifetime judging by the K content in the tissue If hypoxia occurred in the patient s lifetime K content in tissue *decreases* If hypoxia is postmortem K content in the tissue does not change significantly *in contrast to* for example decrease of glycogen or increase of lactic acid This is the advantage of the determination of inorganic ions which are *neither* disintegrated nor synthetized like organic substances and are only transferred from one medium to another if they are not washed out with the blood they remain in tissue long enough to be detected at autopsy Thus the changes in total content of K in tissue are not connected with autolysis but only with lifetime processes During the patient s lifetime hypoxia may be general (in the agonal period for example) and local (for example in the case of the occlusion of one of the coronary arteries) In the case of general hypoxia K content is lowered in all parts of the heart and also in the skeletal muscle and if hypoxia is local K content is reduced only in the area of hypoxia

Thus judging by K distribution in the heart and skeletal muscle we can discover firstly if local ischemia occurred in the patient s lifetime and consequently whether the death was coronary or non coronary and secondly if there was an agonal period and consequently if the death was instantaneous or non instantaneous

If there is no local myocardial ischemia and the death is instantaneous (non coronary death) K on leaving the cell postmortem remains extracel

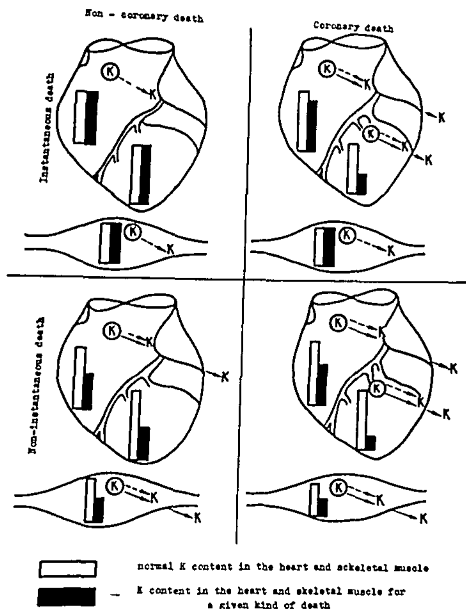


Fig 3 Schematic representation of K distribution in the heart and skeletal muscle in case of instantaneous and non instantaneous coronary and non coronary death (*Unbroken line* = K efflux in ones lifetime *dotted line* = postmortem efflux of K)

lular owing to a discontinued blood flow thus its concentration in the heart and skeletal muscle does not change (Fig 3*A*) In the case of non coronary and non instantaneous death K on leaving the cell in the patient s lifetime during the agonal period while blood flow is maintained is washed out with blood so concentration in all parts of the heart and in the skeletal muscle is lowered (Fig 3*B*)

If there is local myocardial ischemia (coronary death), besides differences in K distribution demonstrated earlier[11] and expressed in inhomogeneous distribution of K in various parts of the heart and skeletal muscle differences also exist depending on the length of time it took the patient to die The heterogeneity in K distribution in the heart will be more pronounced in the case of instantaneous coronary death K content will be considerably reduced in the areas of ischemia in which K efflux takes place in the patient s lifetime while the circulation is being maintained and extracellular K is being washed out with the blood K concentration in non ischemic areas and in the skeletal muscle will be almost unchanged as in the case of an instantaneous cessation of blood flow K on leaving the cell postmortem is not washed out with the blood (Fig 3*C*) Non instantaneous coronary death is characterized by a lesser heterogeneity in K distribution than is instantaneous coronary death K content will be even lower in the areas of local ischemia because K is not only washed out as a result of ischemia but also during the agonal period (Fig 3*D*) Significant reduction of K

content will be seen also in non ischemic parts of the heart and in the skeletal muscle as a result of its removal during the agonal period

The data on the frequency of ventricular fibrillation gathered in Krasnoyarsk give an opportunity to point out the main danger for patients with acute ischemic heart disease Not so long ago physicians in hospital considered heart failure and cardiogenic shock which are the main causes of hospital deaths from acute ischemic heart disease to be the main causes of total deaths from this disease Experimental data[4] showing that high occlusion of the left coronary artery leads to ventricular fibrillation and the sudden death of 60 to 75 per cent of animals and that the coronary artery occlusion lowers the threshold of *fibrillation* had not been taken into account by them for a long time

The situation was changed as two facts came to light (1) epidemiological studies showed that three quarters of patients dying of acute ischemic heart disease perish suddenly before arriving at a clinic Hence it is highly probable that the makeup of the hospital mortality rate does not coincide with the makeup of the total mortality rate from ischemic heart disease and that the complication leading to sudden death is the main one and (2) monitoring studies in coronary care units showed that as a *rule patients suffering* from myocardial infarction die suddenly due to ventricular fibrillation It follows that the main cause of sudden death out of hospital is ventricular fibrillation However the percentage of ventricular fibrillation in acute ischemic heart disease was up to this point unknown There was no opportunity to determine it directly therefore in order to establish the number of cases of sudden death from ventricular fibrillation an indirect method was used The data obtained showed that of all cases of ventricular fibrillation only 6 per cent take place in hospital This is in agreement with the conclusions of Lown and colleagues that even if all clinical *patients with* ventricular fibrillation were reanimated it would only slightly lower the total mortality rate from acute ischemic heart disease

The data received also demonstrate that one fourth of all patients with acute ischemic *heart* disease and two thirds of all dying of *it perish* from ventricular fibrillation It follows that (1) ventricular fibrillation is the prior danger for the patient with acute ischemic heart disease and (2) the major researches in this field must be directed at the search for the means of prevention of ventricular fibrillation

Summary

The reasons for the absence of the exact data on the frequency of sudden death from ventricular fibrillation in patients with acute ischemic heart disease are considered The method for the postmortem diagnosis of ventricular fibrillation occurring out of hospital by exclusion of other causes of sudden coronary death (heart rupture thromboembolism heart failure and cardiogenic shock) is suggested Heart rupture and thromboembolism are excluded at autopsy Ventricular fibrillation (instantaneous death) is differentiated from heart failure and cardiogenic shock (non instantaneous death) on the basis of the length of time it takes the patient to die which is determined by K and Na distribution in the myocardium and skeletal muscle This was studied in four groups of people who died both instantaneously and non *instantaneously* both from coronary and from non coronary diseases The main sign of coronary death was the local decrease in concentration of K in the left ventricle Instantaneous coronary death was characterized by an almost normal content of K in the skeletal muscle and non instantaneous coronary death was characterized by a *decrease of K* content both in the left *ventricle* and in the skeletal muscle Possible reasons for these differences are discussed The frequency of out of *hospital sudden* death was studied in Krasnoyarsk during a three year period by the above method and *compared* with the same frequency of deaths occurring in hospital

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Frequency and significance of conduction defects in acute myocardial infarction

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Following myocardial infarction impairment of cardiac conduction may occur at different sites While damage to the A V node or bundle of His causes atrioventricular block more distal lesions result in bundle branch or intraventricular block The adverse significance of bundle branch block occurring in patients with acute myocardial infarction has been known for many years and has been amply confirmed The terms left anterior and left posterior hemiblock were introduced by Rosenbaum and associates in 1968 to describe block of the anterosuperior or postero inferior divisions of the left main bundle These lesions may occur in isolation or combined with interruption of the right main bundle While the incidence and mortality of left anterior hemiblock and right bundle branch block in acute myocardial infarction have been reported by several authors the frequency and significance of the other common forms of intraventricular conduction disturbances are less well established The present study was undertaken to ascertain the frequency of bundle branch block and hemiblock in a large series of patients with acute myocardial infarction and the associated mortality rate

Patients and methods

The hospital records of 1 085 consecutive admissions to the Coronary Care Unit (C C U) at Aberdeen Royal Infirmary were examined and the number of patients with confirmed myocardial infarction was established A diagnosis of acute infarction was sustained if there was a typical history in combination with definite electrocardiographic changes and/or a significant rise in serum aspartate aminotransferase

Routine admission to the C C U was restricted to patients under 65 years of age with symptoms of less than 24 hours duration but patients of any age suffering from a serious arrhythmia were also admitted All patients remained in the C C U for at least 48 hours and during this period serial 12 lead electrocardiograms and continuous electrocardiographic monitoring were performed Arrhythmias and cardiac failure were treated along standard lines and transvenous cardiac pacemakers were inserted in patients developing second degree (excluding Mobitz type I) or complete A V block Pacemakers were not inserted prophylactically in patients with bundle branch block or left fascicular block

Disturbances of intraventricular conduction on the electrocardiogram were noted during admission and the numbers and outcome of patients suffering the individual types of disturbance was subsequently collated

The electrocardiographs and hospital records of these patients were critically reviewed and the criteria of Julian and colleagues were strictly applied The number of deaths between admission and final discharge from hospital was determined The significance of the results was assessed using the chi square test

Results

Five hundred and fifty six patients had definite evidence of myocardial infarction and there were 94 deaths giving an over all hospital mortality rate of 16.9 per cent The mean age was 56 9 years

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Table I Incidence and mortality of I V conduction disturbance in 556 consecutive patients with acute myocardial infarction

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RBBB	8	1 4	3	37 5
LAH	72	13 0	9	12 5
LPH	32	5 8	6	18 8
RBBB + LAH	34	6 1	24	70 6
RBBB + LPH	25	4 5	12	48 0

Abbreviations LBBB = left bundle branch block RBBB = right bundle branch block LAH = left anterior hemiblock LPH = left posterior hemiblock

Table II Progression to complete A V block

Conduction status	*No of patients*	*No developing complete heart block*	*No of deaths in those developing complete heart block*
Patients with no evidence of prior conduction defect	*362*	*25 (6 9%)*	*7 (28 0%)*
Patients with pre existing I V C D	194	26 (13 4%)	21 (80 8%)
LBBB	23	2 (8 7%)	2 (100%)
RBBB	8	0	—
LAH	72	0	—
LPH	32	3 (9 4%)	2 (66 6%)
RBBB + LAH	34	14 (41 2%)	13 (92 9%)
RBBB + LPH	25	7 (28 0%)	4 (57 1%)

Abbreviations I V C D = intraventricular conduction defect LBBB = left bundle branch block RBBB = right bundle branch block LAH = left anterior hemiblock LPH = left posterior hemi block

with a range from 35 to 82 years though only 9 5 per cent were over 65 years Three hundred sixty two patients (65 1 per cent) had no evidence of intraventricular conduction disturbance (I V C D) and in this group 26 patients died (7 2 per cent) In the 194 patients (34 9 per cent) with some form of I V C D (Mean age 57 5 years) there were 68 deaths (35 1 per cent) indicating a significant increase in mortality in this group ($p < 0\,001$)

The frequency of the various types of I V C D are summarized in Table I Complete left bundle branch block (L B B B) occurred in only 4 1 per cent of patients but had a high mortality rate (61 per cent) This was significantly greater than the mortality rate in the whole group or those with normal conduction ($p < 0\,001$) The most common defect was left anterior hemiblock (L A H) (*13 per cent*) This was associated with a mortality rate of 12 per cent which was not significantly different from those patients with *normal conduction Left posterior hemiblock* (L P H) as an isolated abnormality was much less common (5 8 per cent) but was accompanied by a higher mortality rate (19 per cent), although this also was not statistically significant

Right bundle branch block (R B B B) was the least common defect to occur in isolation (1 6 per cent) and carried a 38 per cent mortality rate It occurred more frequently in conjunction with L A H (6 1 per cent) or L P H (4 5 per cent) Such bifascicular block had a higher mortality rate than a hemiblock or R B B B alone In particular the concurrence of L A H and R B B B seemed to produce a higher mortality rate (71 per cent) than either defect in isolation, although the small number of patients with lone R B B B did not allow statistical validity to be established

Complete A V block developed in 51 patients giving a frequency of 9 2 per cent for the whole series It occurred in 25 (6 9 per cent) of those patients with no prior evidence of intraventricular conduction disturbance and in 26 (13 4 per cent) where I V C D was already present Pro

Table III Results of transvenous pacing in patients who developed complete A V block

Conduction status	*Paced*		*Not Paced*	
	No of survivors	*No of deaths*	*No of survivors*	*No of deaths*
Patients with no evidence of prior conduction defect	15	6	3	1
Patients with pre existing I V C D *	5	14	0	7
I BBB	0	1	0	1
RBBB	0	0	0	0
LAH	0	0	0	0
LPH	1	1	0	1
RBBB + LAH	1	9	0	4
RBBB + LPH	3	3	0	1

Abbreviations I V C D = intraventricular conduction defect LBBB = left bundle branch block RBBB = right bundle branch block I AH = left anterior hemiblock LPH = left posterior h mi block

Table IV Previous reports of the frequency and associated mortality of conduction defects in patients with acute myocardial infarction

Authors	*Year*	*No of patients*	*LBBB*	*RBBB*	*LAH*	*LPH*	*RBBB + LAH*	*RBBB + LPH*
Marriott and Ho an	1970	250	–	–	11 0% (18%)	1% (0)	4 0% (33%)	–
Roos and Dunning	1970	114	–	–	–	–	8 7% (48%)	0 88 (100%)
Godman Alpert and Julian	1971	1809	–	–	–	–	2 8% (59%)	1 1% (80%)
Col and Weinberg	1972	21?	3 7% (63%)	–	9 4% (25%)	–	5 [illegible]% (42%)	1 0% (50%)
Norris Mercer and Croxson	19 [illegible]	1140	–	2 5% (64%)	–	–	2 4% (74%)	0 5% (83%)
Kincaid and Botti	1972	2?5	–	–	6 ?% (7 1%)	–	–	–
Scheinman and Brenman	1972	480	6 6% (4?%)	3 [illegible]% (44%)	4 0% (35%)	0 2% (100%)	4 8% (35%)	0 83% (50%)
Rizzon Di Biase and Baissus	1974	3 5	2 0% (33%)	3 4% (18%)	12 6% (1?%)	0.3% (–)	4 3% (36%)	1 3% (5%)
Nimetz et al	1975	875	2 3% (65%)	1 4% (15%)	– –	–	3 6% (35%)	0 68% (66%)

Frequ ncy expressed as percentage of total series fig res in b ack ts gi percent mortality f r each lesi n

gression to complete heart block was most frequent in patients with L A H and R B B B (41 per cent) Mortality in patients who developed complete heart block was significantly increased whether or not a preceding I V C D was present (p < 0 001) The increase was however much greater in patients with preceding conduction disturbance (80 8 per cent) (Table II) In this series transvenous pacing electrodes were inserted in 40 of the 51 patients with complete A V block but this did not seem to affect noticeably the high mortality rate (Table III)

Discussion

The results of the present study once again highlight the serious implications of the development of conduction defects in patients with myocardial infarction This complication is present in more than one third of all patients and is associated with a more than twofold increase in mortality rate The significance and frequency of conduction defects does of course vary with individual lesions The findings of other workers are summarized in Table IV to allow comparison with the present series Complete left bundle branch block is relatively uncommon occurring in 2 to 6 per cent of cases and our experience agrees with others that it is accompanied by a mortality rate of more than 60 per cent Partial impairment of the left bundle in the form of left anterior hemiblock was the most common conduction defect The mortality rate associated with this defect in isolation has been variable but most reports agree with the present series that it is relatively benign Left posterior hemiblock was found more commonly in our patients than in most other series and appeared to have a worse prognosis than left anterior hemiblock The reason for the increased frequency is difficult to explain Great care was taken in the interpretation of this feature in the electrocardiogram and the criteria were strictly followed None of the patients had right ventricular hypertrophy and evidence of lateral infarction excluded the diagnosis For these reasons it is felt that the high incidence of left posterior hemiblock is not due to over reporting of the condition

Complete right bundle branch was the least common defect to occur in isolation in our series This lesion is frequently considered relatively benign but we found it was associated with a high mortality rate and this has also been clearly shown by other authors Right bundle branch block accompanied by left anterior hemiblock was found much more frequently than isolated right bundle branch block and was the commonest form of bilateral bundle branch block It was again confirmed that this combination is poten

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LAH	72	13 0	9	12.5
LPH	32	5 8	6	18.8
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Roos and Dunning*	19[illegible]0	114	–	–	–	–	8.7% (49%)	0.88% (100%)
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Kincaid and Botti	1972	2[illegible]5	–	–	6.2% (71%)	–	–	–
Scheinman and Brenman	19[illegible]	460	6.6% (47%)	3.[illegible]% (44%)	4.0% (35%)	0.2% (100%)	4.8% (3[illegible]%)	0.83% (50%)
Rizzon, Di Biase and Baissus	1974	325	2.0% (33%)	3.4% (18%)	12.6% (17%)	0.3% (–)	4.3% (36%)	1.3% (75%)
Nimetz et al	1975	8[illegible]5	2.3% (65%)	1.4 (15%)	– –	–	3.6% (35%)	0.68% (66%)

Frequency expressed as percentage of total series, figures in brackets give per cent mortality for each lesion.

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RBBB + LPH	25	7 (28 0%)	4 (57 1%)

Abbreviations I V C D = intraventricular conduction defect LBBB = left bundle branch block RBBB = right bundle branch block LAH = left anterior hemiblock LPH = left posterior hemiblock

with a range from 35 to 82 years though only 9 5 per cent were over 65 years Three hundred sixty two patients (65 1 per cent) had no evidence of intraventricular conduction disturbance (I V C D) and in this group 26 patients died (7 2 per cent) In the 194 patients (34 9 per cent) with some form of I V C D (Mean age 57 5 years) there were 68 deaths (35 1 per cent) indicating a significant increase in mortality in this group ($p < 0.001$)

The frequency of the various types of I V C D are summarized in Table I Complete left bundle branch block (L B B B) occurred in only 4 1 per cent of patients but had a high mortality rate (61 per cent) This was significantly greater than the mortality rate in the whole group or those with normal conduction ($p < 0.001$) The most common defect was left anterior hemiblock (L A H) (13 per cent) This was associated with a mortality rate of 12 per cent which was not significantly different from those patients with normal conduction Left posterior hemiblock (L P H) as an isolated abnormality was much less common (5 8 per cent) but was accompanied by a higher mortality rate (19 per cent), although this also was not statistically significant

Right bundle branch block (R B B B) was the least common defect to occur in isolation (1 6 per cent) and carried a 38 per cent mortality rate It occurred more frequently in conjunction with L A H (6 1 per cent) or L P H (4 5 per cent) Such bifascicular block had a higher mortality rate than a hemiblock or R B B B alone In particular the concurrence of L A H and R B B B seemed to produce a higher mortality rate (71 per cent) than either defect in isolation although the small number of patients with lone R B B B did not allow statistical validity to be established

Complete A V block developed in 51 patients giving a frequency of 9 2 per cent for the whole series It occurred in 25 (6 9 per cent) of those patients with no prior evidence of intraventricular conduction disturbance and in 26 (13 4 per cent) where I V C D was already present Pro

Table III Results of transvenous pacing in patients who developed complete A V block

Conduction status	Paced		Not Paced	
	No of survivors	No of deaths	No of survivors	No of deaths
Patients with no evidence of prior conduction defect	15	6	3	1
Patients with pre existing I V C D	5	14	0	7
LBBB	0	1	0	1
RBBB	0	0	0	0
LAH	0	0	0	0
LPH	1	1	0	1
RBBB + LAH	1	9	0	4
RBBB + LPH	3	3	0	1

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Table IV Previous reports of the frequency and associated mortality of conduction defects in patients with acute myocardial infarction

Authors	*Year*	*No of patients*	*LBBB*	*RBBB*	*LAH*	*LPH*	*RBBB + LAH*	*RBBB + LPH*
Marriott and Hogan	1970	[illegible]50	–	–	11.0% (18%)	1% (0)	4.0% (33%)	–
Roos and Dunning	19 0	114	–	–	–	–	8.[illegible]% (48%)	0.88% (100%)
Godman, Alpert and Julian	19 1	1809	–	–	–	–	2.8% ([illegible]9%)	1.1% (80%)
Col and Weinberg	19 [illegible]	[illegible]12	3 [illegible] (63%)	–	9.4% ([illegible])	–	5 [illegible] (42%)	1.0% ([illegible]0%)
Norris, Mercer and Croxson	19 2	1140	–	2.[illegible]% (64%)	–	–	2.4% ([illegible]4%)	0 (83%)
Kincaid and Botti	19[illegible]	[illegible]	–	–	6.2% (71%)	–	–	–
Scheinman and Brenman	19[illegible]	480	6.6 (4[illegible]%)	3 [illegible] (44%)	4.0% (3[illegible]%)	0.2% (100%)	4.8% (3[illegible]%)	0.83% (50%)
Rizzon, Di Biase and Baissu	19 4	3[illegible]	2.0% (33%)	3.4% (18%)	1.6% (12%)	0.3% (–)	4.3% (36%)	1.3% ([illegible]%)
Nimetz et al	1975	8	[illegible].3% (65)	1.4% (1[illegible]%)	– –	–	3.[illegible]% (35%)	0.68% (60%)

Frequency expressed as percentage of total series figures in brackets give percent mortality for each lesion.

gression to complete heart block was most frequent in patients with L A H and R B B B (41 per cent) Mortality in patients who developed complete heart block was significantly increased whether or not a preceding I V C D was present ($p < 0.001$) The increase was however much greater in patients with preceding conduction disturbance (80.8 per cent) (Table II) In this series transvenous pacing electrodes were inserted in 40 of the 51 patients with complete A V block but this did not seem to affect noticeably the high mortality rate (Table III)

Discussion

The results of the present study once again highlight the serious implications of the development of conduction defects in patients with myocardial infarction This complication is present in more than one third of all patients and is associated with a more than twofold increase in mortality rate The significance and frequency of conduction defects does of course vary with individual lesions The findings of other workers are summarized in Table IV to allow comparison with the present series Complete left bundle branch block is relatively uncommon occurring in 2 to 6 per cent of cases and our experience agrees with others that it is accompanied by a mortality rate of more than 60 per cent Partial impairment of the left bundle in the form of left anterior hemiblock was the most common conduction defect The mortality rate associated with this defect in isolation has been variable but most reports agree with the present series that it is relatively benign Left posterior hemiblock was found more commonly in our patients than in most other series and appeared to have a worse prognosis than left anterior hemiblock The reason for the increased frequency is difficult to explain Great care was taken in the interpretation of this feature in the electrocardiogram and the criteria were strictly followed None of the patients had right ventricular hypertrophy and evidence of lateral infarction excluded the diagnosis For these reasons it is felt that the high incidence of left posterior hemiblock is not due to over reporting of the condition

Complete right bundle branch was the least common defect to occur in isolation in our series This lesion is frequently considered relatively benign but we found it was associated with a high mortality rate and this has also been clearly shown by other authors Right bundle branch block accompanied by left anterior hemiblock was found much more frequently than isolated right bundle branch block and was the commonest form of bilateral bundle branch block It was again confirmed that this combination is poten

tially very serious and is associated with a very high mortality rate Right bundle branch block together with left posterior hemiblock was much less frequent, although less rare than in other series Previous reports have suggested a very poor prognosis with this form of bifascicular block[1] but in the present series, although mortality was high it was less than that for right bundle branch block with left anterior hemiblock

From our figures it is clear that the development of complete heart block is as might be expected, more frequent in patients with preexisting evidence of conduction defect It is particularly prone to occur in the presence of bifascicular block and our findings are in agreement with others in this respect Complete heart block in this situation is prognostically grave with a mortality rate in excess of 80 per cent despite the use of transvenous pacing

The results of this study are important clinically from two main aspects Firstly, it is helpful to know the prognosis in patients in whom acute myocardial infarction is accompanied by a conduction defect Many patients with such defects are initially relatively well and may give little clinical indication of the severity of their condition On the other hand the development of left anterior hemiblock, a common occurrence, has now been shown not to be associated with an increased mortality rate and should only give cause for concern if accompanied by other conduction defects Secondly this series has again demonstrated the frequency with which conduction defects and in particular bifascicular block may progress to complete A V block and it is particularly in these patients that mortality is so greatly increased It has recently been suggested that His bundle electrograms carried out in patients with bilateral bundle branch block will assist in identifying those patients most likely to develop complete heart block Unfortunately prophylactic pacing in these selected patients failed to reduce mortality[1] It is therefore questionable whether this technique which is not without arrhythmic complications should be undertaken in all patients with bilateral bundle branch block At present therefore controversy persists as to whether there is benefit from prophylactic insertion of a temporary pacemaker Pacing was not carried out prophylactically in the present series, but catheters were inserted rapidly as soon as complete heart block developed with apparently disappointing results On the other hand, of the five patients who did survive the development of complete heart block accompanying bifascicular block all received a period of temporary pacing It is not possible from our results to be certain whether such treatment is of value and there would seem to be an indication for a prospective random trial of pacing in the treatment of patients with bifascicular block It must be noted, however that many patients with widespread conduction defects were in severe left heart failure and died as a result of this In these patients the occurrence of complete heart block, if it took place at all was a terminal event and pacing could not assist

In summary, therefore our results indicate a good outlook in patients who have no evidence of conduction defect but an increasingly grave prognosis as the degree of block increases from a unifascicular block to a bifascicular block The development of complete heart block has been shown to be much commoner in these patients and to be accompanied by a high mortality rate when it develops whether or not artificial pacing is rapidly carried out

Summary

The frequency of intraventricular conduction defects was determined in 556 consecutive patients with proven acute myocardial infarction Complete left bundle branch block was present in 23 patients and carried a high mortality rate (61 per cent) Complete right bundle branch block was the rarest defect to be seen in isolation (8 patients) and carried a lower mortality rate (38 per cent) Lone left anterior hemiblock was present in 72 patients and was associated with a low mortality rate (13 per cent) Left posterior hemiblock occurred in 32 patients (mortality rate 19 per cent) In a further 59 patients right bundle branch block with left anterior or posterior hemiblock in addition was present and these patients had a high mortality rate which was greater than isolated right bundle branch block or hemiblock alone Complete atrioventricular block developed in 51 patients 26 of whom had prior evidence of intraventricular conduction defect Despite the use of temporary transvenous pacing mortality in patients who developed complete heart block was significantly increased whether or not an intraventricular conduction defect was already

present The significance of these findings for the management of patients with myocardial infarction is discussed

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The supra-additive natriuretic effect addition of theophylline ethylenediamine and bumetanide in congestive heart failure

Permutation trial tests in patients in long term treatment with bumetanide

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In the management of advanced heart failure combinations of diuretics with different renal tubular actions are often useful[1] In previous communications we have demonstrated a supra additive natriuretic effect addition of thiazide diuretics (bendroflumethiazide or quinethazone) and potent diuretics (furosemide or bumetanide) in patients with congestive heart failure receiving long term treatment with potent diuretics [2,3]

As a tentative explanation of this striking interaction between two types of diuretics the following hypothesis was advanced During long term treatment with a potent diuretic the depression of renal tubular sodium reabsorption at some sites in the nephron induces an accelerated sodium reabsorption at more distal sites because of increased supply of sodium and because of activation of homeostatic mechanisms for sodium conservation In this setting the administration of a small dose of a thiazide diuretic will be able to promote a supra additive natriuresis through its effect at the sites of accelerated sodium reabsorption

According to this hypothesis a similar response should be expected if patients receiving long term treatment with a potent diuretic are given an other type of diuretic which has a natriochloruretic effect similar to the thiazides but exerts its action at least in part at different sites in the nephron e g theophylline ethylenediamine[4,5] The present study is designed to examine if theophylline ethylenediamine is able to produce a supra additive natriuretic effect in patients with congestive heart failure during long term treatment with bumetanide

Material and methods

The patients comprised 18 adult subjects with organic heart disease and signs of congestive heart failure requiring more intensive diuretic treatment The series included 16 females and two males Fifteen subjects had valvular heart disease, two subjects had ischemic heart disease and one had cardiomyopathy All patients had received digoxin and bumetanide or thiazides previously

The studies were performed during admission to hospital after a stabilization period of three days The patients received a three Gm sodium chloride diet with the supplement of three Gm potassium chloride and 1500 milliliters fluid per day Treatment with digoxin was continued

Twenty four hour urines were collected at 7 A M and a fasting blood sample for measurement of serum osmolality was taken every morning The body weights were measured every morning in pyjamas in the fasting state and after initial A M voiding and the urine was examined for sodium potassium chloride creatinine and osmolality Osmolal and free water clearances were calculated as described previously[6]

Since the response to diuretic treatment varies not only with the drugs used but also with the

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Table I Sequence of administration of diuretic treatments

No of patients	Days of treatment		
	First	Second	Third
1	A	B	C
1	A	C	B
1	B	A	C
1	B	C	A
1	C	A	B
1	C	B	A

F e planation of A B a d C see te t

pathophysiologic status of the patient and with the sequence of administration of drugs the design of the study aimed at minimizing the effects of the latter variables The study was performed as permutation trial tests in which the drug treatment followed the rotation scheme shown in Table I This type of program ensures that within each trial all treatments are given to each patient and that each treatment has an equal chance of being used on the first second or third day of the trial A random allocation of patients to treatment programs was secured

Trial I comprised six patients receiving long term treatment with bumetanide 2 mg b i d and compared the effect of the combination of theophylline ethylenediamine 400 mg + bumetanide 4 mg (A) with the effect of bumetanide 4 mg (B) and the effect of bumetanide 6 mg (C)

Trial II comprised 6 patients receiving long term treatment with bumetanide 2 mg twice a day and compared the effect of the combination of theophylline ethylenediamine 400 mg plus bumetanide 4 mg (A) with the effect of theophylline ethylenediamine 400 mg alone (B) and the effect of bumetanide 4 mg alone (C)

Trial III comprised six patients previously treated with a thiazide diuretic and compared the effect of theophylline ethylenediamine 400 mg plus bumetanide 2 mg (A) with the effect of theophylline ethylenediamine 400 mg alone (B) and with the effect of bumetanide 2 mg alone (C)

The drugs used were administered as follows Bumetanide was given in two doses 1 2 or 3 mg at 9 A M and 1 2 or 3 mg at 1 P M Theophylline ethylenediamine was given as 200 mg at 9 A M and 200 mg at 1 P M

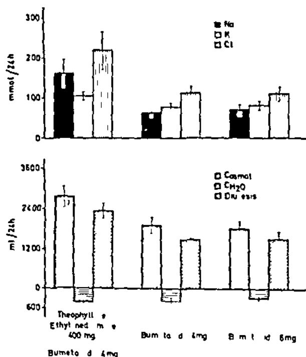


Fig 1 Mean values for twenty four hour urinary electrolyte and water excretion in relation to diuretic treatments in Trial I Vertical bars indicate ±1 SEM In cardiac patients receiving long term treatment with bumetanide 4 mg daily a single day s treatment with theophylline ethylenediamine 400 mg induces a significantly higher electrolyte and water excretion than additional bumetanide

Statistical analysis was performed by means of the Wilcoxson test for pair differences P values less than 0 05 were considered statistically significant

Terminology Dose addition describes the combined effects of two drugs acting on the same receptors if doses of one drug are able to substitute for those of the other in proportion to their relative potency Deviations from dose addition are termed supra additive or infra additive and usually imply that the drugs act by different mechanisms

Effect addition or summation describes the combined effects of two drugs acting through different mechanisms when the response is equal to the sum of their individual effects Deviations from effect addition are usually termed supra additive or infra additive

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The drugs used were administered as follows: Bumetanide was given in two doses, 1, 2, or 3 mg at 9 A.M. and 1, 2, or 3 mg at 1 P.M. Theophylline ethylenediamine was given as 200 mg at 9 A.M. and 200 mg at 1 P.M.

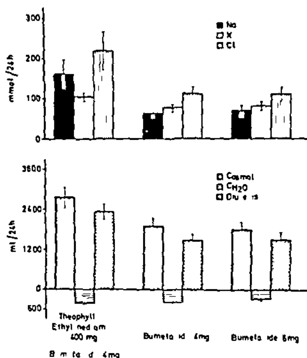


Fig. 1. Mean values for twenty-four hour urinary electrolyte and water excretion in relation to diuretic treatments in Trial I. Vertical bars indicate ±1 SEM. In cardiac patients receiving long term treatment with bumetanide 4 mg daily a single day's treatment with theophylline ethylenediamine 400 mg induces a significantly higher electrolyte and water excretion than additional bumetanide.

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Results

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Table II Statistical analysis of renal electrolyte water and solute excretion and of weight loss in Trial I

Urinary excretion	Units	*Mean 24 hour values ± S E M*			*Statistical significance of differences*	
		Theophylline ethylenediamine 400 mg + bumetanide 4 mg (A)	*Bumetanide 4 mg (B)*	*Bumetanide 6 mg (C)*	*A B*	*A C*
Sodium	mmol /24 hours	163 ± 36	67 ± 12	71 ± 14	x	x
Potassium	mmol /24 hours	105 ± 9	77 ± 11	80 ± 11	x	x
Chloride	mmol /24 hours	219 ± 48	113 ± 17	111 ± 18	ns	x
Diuresis	ml /24 hours	2328 ± 243	1467 ± 182	1507 ± 223	x	x
Osmolal clearance	ml /24 hours	2755 ± 308	1885 ± 235	1796 ± 237	x	x
Free water clearance	ml /24 hours	−428 ± 140	−419 ± 124	−289 ± 51	ns	ns
Creatinine	mmol /24 hours	9.08 ± 0.51	9.33 ± 0.51	7.85 ± 0.64	ns	ns
Weight loss	kg /24 hours	−1.16 ± 0.14	−0.15 ± 0.00	−0.25 ± 0.26	x	ns
Creatinine clearance	ml /min	65 ± 4	65 ± 5	55 ± 7	ns	ns

ns $p > 0.05$ x $p < 0.05$

Table III Statistical analysis of renal electrolyte, water and solute excretion and of weight loss in Trial II

Urinary excretion	Units	*Mean 24 hour values ± S E M*			*Statistical significance of differences*	
		Theophylline ethylenediamine 400 mg + bumetanide 4 mg (A)	*Theophylline ethylenediamine 400 mg (B)*	*Bumetanide 4 mg (C)*	*A B*	*A C*
Sodium	mmol /24 hours	203 ± 26	12 ± 4	95 ± 10	x	x
Potassium	mmol /24 hours	105 ± 13	63 ± 7	94 ± 12	x	ns
Chloride	mmol /24 hours	245 ± 25	7 ± 2	140 ± 14	x	x
Diuresis	ml /24 hours	2463 ± 166	1038 ± 224	1833 ± 181	x	ns
Osmolal clearance	ml /24 hours	2915 ± 199	1557 ± 242	2253 ± 197	ns	ns
Free water clearance	ml /24 hours	−454 ± 85	−519 ± 147	−420 ± 62	ns	ns
Creatinine	mmol /24 hours	9.05 ± 0.75	9.30 ± 1.57	9.78 ± 1.65	ns	ns
Weight loss	Kg /24 hours	−1.33 ± 0.22	−0.06 ± 0.20	−0.35 ± 0.24	x	x
Creatinine clearance	ml /min	62 ± 8	61 ± 6	55 ± 5	ns	ns

ns $p > 0.05$ x $p < 0.05$

ide 4 mg (B) and of bumetanide 6 mg (C) in six patients (Fig 1) The results are shown with statistical analysis in Table II

A Theophylline ethylenediamine 400 mg plus bumetanide 4 mg compared to bumetanide 4 mg (comparison A B) The renal excretion of sodium potassium and water osmolal clearance and weight loss were significantly higher after supplementary theophylline ethylenediamine than without this drug ($p < 0.05$) The creatinine clearance was unaffected

B Theophylline ethylenediamine 400 mg plus bumetanide, 4 mg compared to bumetanide 6 mg (comparison A C) Supplementary theophylline ethylenediamine resulted in a significantly higher excretion of sodium potassium chloride, water and osmolal clearance than found after additional bumetanide 2 mg ($p < 0.05$) Creatinine clearance was unchanged

Trial II This trial compared the effects of theophylline ethylenediamine 400 mg plus bumetanide 4 mg (A) of theophylline ethylene

Table IV Net effects of combination of drugs in Trial II (A [B+C])

Parameters	Units	Mean ± S.E.M (A)	Mean ± S.E.M (B + C)	Statistical significance of differences (A [B+C])
Urinary sodium	mmol/24 hours	203 ± 26	107 ± 9	p < 0.05
Urinary chloride	mmol/24 hours	245 ± 25	147 ± 10	p < 0.05

For explanation of A, B and C see Table III and text.

diamine 400 mg (B) and of bumetanide 4 mg (C). The results are shown in Tables III through IV and in Fig 2.

A Theophylline ethylenediamine 400 mg plus bumetanide 4 mg compared to theophylline ethylenediamine 400 mg (comparison A B). The renal excretion of sodium potassium chloride and water and the weight loss were significantly higher after the combination of drugs than after theophylline ethylenediamine ($p < 0.05$). Creatinine clearance was unchanged.

B Theophylline ethylenediamine 400 mg and bumetanide 4 mg compared to bumetanide 4 mg (comparison A C). Similar to the findings above urinary output of sodium and chloride and weight loss were significantly higher after supplementary theophylline ethylenediamine than without this drug ($p < 0.05$).

C Net effects of the combination of drugs. The differences (A – [B + C]) i.e. the response to the combination of drugs minus the sum of the responses to individual drugs calculated for each patient are assumed to represent the net effects of the combination of diuretics. Actually this estimate presumes that urinary excretion is equal to zero without treatment and it seems likely therefore that the net effects are underrated. Nevertheless in terms of urinary sodium and chloride outputs the differences (A – [B + C]) are positive and statistically significantly different from zero ($p < 0.05$) (Table IV).

These results clearly indicate that the effects of the combination of theophylline ethylenediamine and bumetanide in this setting represent a supra additive natriuretic effect addition.

Trial III This trial compared the effects of theophylline ethylenediamine 400 mg plus bumetanide 2 mg (A) of theophylline ethylenediamine 400 mg (B) and of bumetanide 2 mg (C) (Fig 3). No significant differences were found in excretion of water or electrolytes whether theophylline ethylenediamine was added to bumetanide or not in patients who were not receiving long term treatment with bumetanide.

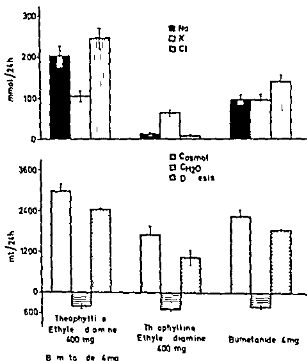


Fig 2 Mean values for twenty four hour urinary electrolyte and water excretion in relation to diuretic treatments in Trial II. Vertical bars indicate ±1 S.E.M. In cardiac patients receiving long term treatment with bumetanide 4 mg daily the natriuretic and chloruretic response to a single days combination of theophylline ethylenediamine and bumetanide is significantly higher than the sum of the responses to the single drugs.

Discussion

The first trial demonstrates clearly that in patients receiving long term treatment with bumetanide supplementary theophylline ethylenediamine given orally results in an additive natriuretic and diuretic effect which is far superior to that of additional bumetanide. From the second trial it appears that the additive natriuretic effect is a supra additive effect addition of theophylline ethylenediamine and bumetanide. As shown in the third trial this effect can not be obtained in patients who have not previously received bumetanide for some time.

Apparently the natriuretic effect of supple

Table II Statistical analysis of renal electrolyte water and solute excretion and of weight loss in Trial I

Urinary excretion	Units	Mean 24 hour values ± S.E.M. Theophylline ethylenediamine 400 mg + bumetanide 4 mg (A)	Bumetanide 4 mg (B)	Bumetanide 6 mg (C)	Statistical significance of differences A B	A C
Sodium	mmol /24 hours	163 ± 36	67 ± 12	71 ± 14	x	x
Potassium	mmol /24 hours	105 ± 9	77 ± 11	80 ± 11	x	x
Chloride	mmol /24 hours	219 ± 48	113 ± 17	111 ± 18	ns	x
Diuresis	ml /24 hours	2328 ± 243	1467 ± 182	1507 ± 223	x	x
Osmolal clearance	ml /24 hours	2755 ± 308	1885 ± 235	1796 ± 237	x	x
Free water clearance	ml /24 hours	−428 ± 140	−419 ± 124	−289 ± 51	ns	ns
Creatinine	mmol /24 hours	9.08 ± 0.51	9.33 ± 0.51	7.85 ± 0.64	ns	ns
Weight loss	kg /24 hours	−1.16 ± 0.14	−0.15 ± 0.00	−0.25 ± 0.26	x	ns
Creatinine clearance	ml /min	65 ± 4	65 ± 5	55 ± 7	ns	ns

ns $p > 0.05$ x $p < 0.05$

Table III Statistical analysis of renal electrolyte, water and solute excretion and of weight loss in Trial II

Urinary excretion	Units	Mean 24 hour values ± S.E.M. Theophylline ethylenediamine 400 mg + bumetanide 4 mg (A)	Theophylline ethylenediamine 400 mg (B)	Bumetanide 4 mg (C)	Statistical significance of differences A B	A C
Sodium	mmol /24 hours	203 ± 26	12 ± 4	95 ± 10	x	x
Potassium	mmol /24 hours	105 ± 13	63 ± 7	94 ± 12	x	ns
Chloride	mmol /24 hours	245 ± 25	7 ± 2	140 ± 14	x	x
Diuresis	ml /24 hours	2463 ± 166	1038 ± 224	1833 ± 181	x	ns
Osmolal clearance	ml /24 hours	2915 ± 199	1557 ± 242	2253 ± 197	ns	ns
Free water clearance	ml /24 hours	−454 ± 85	−519 ± 147	−420 ± 62	ns	ns
Creatinine	mmol /24 hours	9.05 ± 0.75	9.30 ± 1.57	9.78 ± 1.65	ns	ns
Weight loss	Kg /24 hours	−1.33 ± 0.22	−0.06 ± 0.20	−0.35 ± 0.24	x	x
Creatinine clearance	ml /min	62 ± 8	61 ± 6	55 ± 5	ns	ns

ns $p > 0.05$ x $p < 0.05$

ide 4 mg (B) and of bumetanide 6 mg (C) in six patients (Fig 1) The results are shown with statistical analysis in Table II

A Theophylline ethylenediamine 400 mg plus bumetanide, 4 mg compared to bumetanide 4 mg (comparison A B) The renal excretion of sodium, potassium, and water osmolal clearance and weight loss were significantly higher after supplementary theophylline ethylenediamine than without this drug ($p < 0.05$) The creatinine clearance was unaffected

B Theophylline ethylenediamine 400 mg plus bumetanide 4 mg compared to bumetanide 6 mg (comparison A C) Supplementary theophylline ethylenediamine resulted in a significantly higher excretion of sodium potassium chloride water and osmolal clearance than found after additional bumetanide 2 mg ($p < 0.05$) Creatinine clearance was unchanged

Trial II This trial compared the effects of theophylline ethylenediamine 400 mg plus bumetanide 4 mg (A) of theophylline ethylene

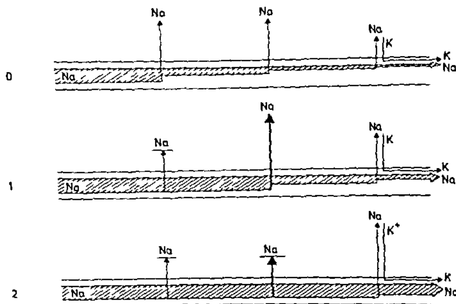


Fig 4 Theoretical schematic diagram of the combined effects of diuretics upon renal tubular sodium transport *Panel 0* illustrates the sodium reabsorption in the untreated patient *Panel 1* depicts the depression of sodium reabsorption during long term treatment with a potent diuretic like bumetanide and the subsequent hyperreabsorption of sodium more distally in the nephron mediated by homeostatic mechanisms The sodium potassium exchange in the distal nephron is accelerated *Panel 2* illustrates the effects of a single day s treatment with a thiazide diuretic during long term treatment with a potent diuretic The thiazide depresses sodium reabsorption at the site of accelerated reabsorption and induces a supra additive natriuresis The sodium potassium exchange mechanisms are further accelerated

were performed in subjects receiving long term therapy with digoxin and bumetanide 4 mg daily In the first trial the response to supplementary theophylline ethylenediamine 400 mg was definitely superior to that of additional bumetanide 2 mg in terms of renal output of sodium chloride potassium water and osmolal clearance In the second trial the comparison was made of the effects of theophylline ethylenediamine 400 mg plus bumetanide 4 mg of theophylline ethylenediamine 400 mg and of bumetanide 4 mg In terms of natriuresis and chloruresis the response to the combination of two drugs was significantly larger than the sum of the effects of other treatments

The third permutation trial test comprised six patients who had not previously received bumetanide In this group no additive natriuretic or diuretic effect could be demonstrated after administration of theophylline ethylenediamine

It is concluded that in patients receiving long term treatment with the potent diuretic bumetanide the combined effects of oral theophylline ethylenediamine and bumetanide represent a supra additive natriuretic and chloruretic effect addition A tentative explanation for the mechanism of interaction of drugs in terms of inhibition of renal tubular sodium transport is given

Since the combined effects of the two drugs involve a tendency to development of increased kaliuresis it is recommended that supplementary use of theophylline ethylenediamine in this setting is combined with the administration of potassium chloride

Apparently oral theophylline ethylenediamine represents an alternative possibility to thiazide diuretics when additional natriuresis and diuresis are required in patients with advanced heart failure on long term treatment with potent diuretics like bumetanide

Bumetanide was supplied by Leo Pharmaceutical Products DK 2750 Ballerup Denmark

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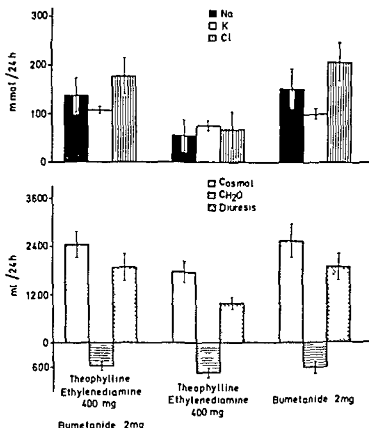


Fig 3 Mean values for twenty four hour urinary electrolyte and water excretion in relation to diuretic treatments in Trial III Vertical bars indicate ±1 S E M In cardiac patients who have not received long term treatment with bumetanide the response to the combination of theophylline ethylenediamine and bumetanide is not significantly different from the response to bumetanide alone

mentary theophylline ethylenediamine can not be ascribed to an increase in glomerular filtration rate as evaluated by means of the twenty four hour creatinine clearance It seems likely there fore that the effect is due to a renal tubular action of theophylline ethylenediamine

The supra additive natriuretic and chloruretic effect addition of theophylline ethylenediamine and bumetanide shown in this study is very similar to that induced by a thiazide diuretic (bendroflumethiazide or quinethazone) in patients receiving long term treatment with furosemide or bumetanide

A tentative explanation of the supra additive effect addition observed is given schematically in Fig 4 The renal tubular reabsorption of sodium represents a sum of multiple discrete functions throughout the nephron A major part is reabsorbed in conjunction with chloride or bicarbonate as represented by the arrows to the left and in the middle of the upper panel of the diagram A minor fraction is reabsorbed in exchange with potassium in the distal tubules as *shown by the arrow to the right*

During the long term administration of a potent diuretic, the drug will depress the reabsorption of sodium in conjunction with chloride at several sites in the nephron and through this effect accelerate sodium reabsorption at more distal sites by means of the increased supply of sodium and by means of homeostatic mechanisms activated during natriuresis This type of action will also accelerate the sodium-potassium exchange in the distal tubules This pattern of action is shown in the middle panel of Fig 4

In this setting it becomes possible for a second less potent diuretic, through its action at the sites of accelerated reabsorption to promote a more marked natriuresis than it would be able to induce when used alone Because of the increased delivery of sodium to the exchange sites and due to activation of homeostatic mechanisms for sodium conservation the potassium excretion in conjunction with chloride is further increased This interaction of drugs is shown in the lower panel of Fig 4

It appears from Tables II and III that supplementary administration of theophylline ethylenediamine in this particular setting results in an increased output of potassium A clinical corollary to this finding is that the supplementary use of theophylline ethylenediamine in patients receiving long term treatment with potent natriuretics involves a risk of development of potassium loss and hypokalemia and an associated risk of precipitation of digitalis toxicity It seems advisable therefore that extra supplements of potassium chloride should be considered in this setting

In conclusion it may be stated that theophylline *ethylenediamine represents an alternative* possibility to thiazide diuretics when additional treatment is required in patients with advanced congestive heart failure receiving long term treatment with a potent diuretic like bumetanide or furosemide

Summary

The additive natriuretic effect of oral theophylline ethylenediamine 400 mg and the potent diuretic bumetanide has been studied in patients with advanced congestive heart failure Two permutation trial tests including six patients each

Cardiovascular effects of dobutamine in severe congestive heart failure

J J Andy M D *
C L Curry M D *
N Ali M D * *
P P Mehrotra** *
Washington D C

Sympathomimetic agents are frequently used in the treatment of refractory cardiac failure However available agents are limited by their tendency to produce potentially deleterious changes in heart rate rhythm and blood pressure A substance that provides an isolated increase in myocardial contractility should prove clinically valuable Dobutamine was synthesized by Tuttle and Mills and early animal studies demonstrated that in the dose range of 5 to 20 µg/Kg /min it is selectively inotropic A comparative study of the effects of dopamine (the only other selective sympathomimetic agent) and dobutamine in dogs showed that dobutamine increased cardiac output to a greater extent than does dopamine The present study was designed to evaluate the effectiveness and safety of dobutamine in patients with severe congestive heart failure

Methods

The effect of dobutamine was assessed hemodynamically echocardiographically and by measurement of the systolic time intervals Seventeen patients (13 males and 4 females) ranging in ages from 21 to 68 years (mean 49 years) consented to the study All had biventricular failure by standard clinical criteria and seven had proved clinically refractory to digoxin and large doses of furosemide The Clinical Status of the patients is presented in Tables I II and III Patients with acute coronary insufficiency cor pulmonale or with frequent or multifocal premature ventricular beats were excluded All drugs were stopped for twelve hours prior to infusion and restarted after three hours of continuous infusion The duration of the infusion ranged from three hours to 172 hours The data reported here were obtained within the first 2¼ hours

Hemodynamic studies Eleven patients consented to right heart catheterization and a Swan Ganz balloon tipped flow directed catheter was advanced to the pulmonary artery (PA) via an antecubital fossa cut down A Seldinger s needle was inserted in the femoral artery

Six patients who did not have complete right heart catheterization had a long polyethylene tube advanced percutaneously to the right atrium Pressures were recorded using Statham P23D6 strain gauge transducers* and an Electronics for Medicine† recorder Blood pressures were obtained with a sphygmomanometer in the six patients who had central venous pressure monitoring Cardiac output (dye dilution) was obtained by injecting cardiogreen 5 mg into the main PA and sampling from the femoral artery through a Gilford Cuvette Densitometer

Control hemodynamic recording was followed by the infusion of dobutamine in a dose of 5 10

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R U	Arterial pressure (mm Hg)	Mean arterial pressure (mm Hg)	S V R H R U	Duration of therapy
	150/130	13	50 8	76
	178/130	146	24 3	
	160/100	1 0	40	97
	150/90	110	22	
	110/90	97	38 8	7_
	108/84	89	21 ?	
	114/90	98	39.2	96
	1?8/90	103	?5 6	
	1?0/100	107	46 5	5 0
	1 0/80	93	25 1	
	120/90	100	–	74
	130/90	103		
	90/60	70	–	118
	90/6?	,0		
	130/90	103	–	172
	150/74	97		
	112/ 0	8?	27 3	~?
	1?0/69	81	17 2	
	10?/65	7	19 5	~2
	100/60	73	10 0	
	100/65	77	?6 5	68
	10?/6?	75	14 1	
± 1 7			36 1 ± 0 08	
± 1 3			19 ? ± 0 6	
S)			p < 0 001	

second and focused at 7 5 cm was used in this study Lead II ECG was simultaneously recorded and the paper speed was 50 cm /sec A control echogram was obtained and dobutamine was infused at 15µg/Kg /min Echocardiogram was repeated 1½ to 2 hours following onset of continuous Dobutamine infusion All tracings were obtained with the patient supine

Echocardiographic left ventricular internal diameters were measured where portions of both mitral leaflets the septum and the posterior left ventricular walls were clearly outlined The maximum amplitude of systolic motion of the left ventricular endocardial echo or posterior wall excursion (P W E) and the maximum rate of rise of the posterior wall endocardial echo or velocity of posterior wall excursion (VPWE) were measured as described by Kraunz and Kennedy in the same area where internal diameters were taken The end diastolic diameter (Dd) was taken as the maximum diameter in diastole and the end systolic diameter (Sd) was the minimum diameter in systole between the septal and posterior wall endocardial surfaces The mean velocity of circumferential fiber shortening (Vcf) was calculated using the formula Dd – Ds/Dd × dt where dt is the duration of contraction In all cases averages were taken of several consecutive measurements

Systolic Time Intervals (S T I) Simultaneous high frequency phonocardiogram electrocardiogram and external carotid pulse tracing were recorded at a paper speed of 100 mm /sec with an Electronics for Medicine D R8 recorder* and a Kodak linograph 1930 paper † The external carotid pulse and phonocardiogram were inscribed with an Electronics for Medicine PS 1 recorders * A control recording was followed by continuous infusion of dobutamine at 15µg/Kg / min Recording was repeated 1½ hours following onset of drug infusion

Left ventricular ejection time (L V E T) was measured from the initial rapid upstroke of the external carotid pulse tracing to the incisura The pre ejection period (P E P) was obtained by subtracting L V E T from the electromechanical systolic interval ($Q S_2$) measured from the initial deflection of the QRS complex to the first high frequency component of the second sound The mean intervals were all corrected for heart rate using the regression equation of Weissler and associates All recorded values were the averages of several consecutive cardiac cycles

Other parameters Complete blood count (C B C) electrolytes creatinine serum glutamic oxaloacetate and pyruvic transaminases (S G O T S G P T) phosphate serum creatinine phosphokinase (C P K) bilirubin as well as urinalysis and microscopy were obtained before drug infusion and were monitored every morning during drug infusion The indices were repeated 24 hours following the termination of the therapy

Following 2 to 2½ hours of acute monitoring in the laboratory the Swanz Ganz catheters were removed pulse and blood pressure were monitored every one hour throughout the duration of therapy ECG s were obtained daily In the six patients who had the CVP measured this index

*Electronics for Medicine Wh te Pla N Y
†Eastma Kod k Rochest r N Y

Table I Hemodynamics (10 to 15 μg/Kg /min)

Name	Age & sex		Heart disease	Dose μg/Kg /min	Heart rate (beats/min)	Mean PAP (mm Hg)	Mean PAWP (mm Hg)	CO (liters/min)	SV (ml/beat)
J I	35	M	HCVD	C	108	47	35	2 7	25
				D 15	132	50	27	6 0	45 5
H P	61	M	HCVD & atrial fibrillation	C	126	32	19	3 08	24 4
				D 15	156	28	14	5 0	32 0
R V	34	M	Cardiomyopathy	C	96	28	18	2 5	24 5
				D 15	112	16	4	4 2	37 5
J E	60	M	Cardiomyopathy	C	108	41	34	2 5	23 1
				D 15	114	45	30	4 0	35 1
C S	31	M	Cardiomyopathy & heart block	C	63	40	30	2 30	36 5
				D 10	54	35	22	3 70	68 5
R A R	47	M	Cardiomyopathy	C	116	45	18	–	–
				D 15	124	32	10		
M Q	58	M	ASHD	C	80	48	35	–	–
				D 10	90	48	26		
J H	60	M	ASHD	C	111	45	31	–	–
				D 10	120	40	25		
J C	55	M	Cardiomyopathy	C	69	43	32	3 0	43 5
				D 10	84	25	23	4 70	56 0
J M	21	F	Cardiomyopathy	C	114	38	37	3 90	34 2
				D 10	111	32	25	7 30	65 8
M N	57	F	Cardiomyopathy	C	96	55	36	2 90	29 8
				D 10	102	45	15	5 30	52 0
Mean				C		42 ± 7	30 ± 7	2 9 ± 0 7	30 ± 6
				D (10 15)		36 ± 11	20 ± 8	5 0 ± 1 2	49 ± 11
						p < 0 02	p < 0 001	p < 0 001	p < 0 00[illegible]

Abbreviations M = male F = female C = control P A P = pulmonary artery pressure P A W P = pulmonary artery wedge pressure C O = cardiac output S V = stroke volume P V R = pulmonary vascular resistance H R U = hybrid resistance unit S V R = systemic vascular resistance H C V D = hypertensive cardiovascular disease A S H D = atherosclerotic heart disease HR = heart rate BP = blood pressure D = dobutamine

and/or 15 μg/Kg /min with repeat hemodynamic measurements every 30 minutes for 2 to 2½ hours For the infusion 100 mg of dobutamine was dissolved and made up to 100 c c with 5 per cent dextrose and water in a soluset Electrocardiogram was monitored continuously for three hours on an Electronics for Medicine eight channel recorder *

Systemic vascular resistance (S V R) in hybrid resistance unit (H R U) was calculated from the formula

$$SVR = \frac{MAP}{CO}$$ (where M A P = mean arterial pressure in mm Hg and

C O = cardiac output in liters/min)

Total pulmonary vascular resistance (P V R) in H R U was calculated from the formula P V R = (M P A P – PAWP)/C O (where M P A P = mean pulmonary artery pressure in mm Hg and C O = cardiac output in liters/min and PAWP = pulmonary artery wedge pressure in mm Hg) The mean arterial pressure in mm Hg (M A P) was calculated as M A P = (systolic blood pressure + 2× diastolic pressure)/3 in the six patients whose blood pressure was measured with the sphygmomanometer

Echocardiographic study A Honeywell Visicorder 1856 echogram strip chart recorder* utilizing a 2 25mHZ transducer with 12 mm crystal with a repetitive rate of 1000 pulses/

Electronics for Medicine White Plains N Y

Honeywell Denver Colo

Table III Echocardiogram

Name	*Age & sex*	*Heart disease*	*Dose (µg/Kg/min)*	*Dd (cm)*	*Ds (cm)*	*VPWE (cm/sec)*	*PWE (cm)*	*dt (secs)*	*Mean Vcf (circ/sec)*	*CVP PAWP (mm Hg)*	*Duration of therapy (hours)*
H C	56 M	HCVD	C	6 54	5 77	3 00	0 930	0 263	0 447	13 0	
			D 15	6 44	,78	3 33	0 9,0	0 264	0.388	6 0	44
S H	68 M	ASHD	C	7 43	6.20	2 6?	0 ,8	0 263	0 571	16 0	
			D 15	6 5?	5 40	4 8	0 9,0	0 2635	0 635	7 0	69
S G	53 F	Cardiomyopathy	C	7 170	6.23	3 66	1 060	0 224	0 587	?6	
			D 15	7 040	6 0?	3 48	1 000	0 2 0	0.598	13	46
J I	35 M	HCVD	C	5 61	4 95	4 20	0.580	0.269	0 437	35	
			D 15	5 30	4 80	6 28	0 714	0 235	0 436	2,	?6
R V	34 M	Cardiomyopathy	C	7 310	6 68	2 42	0 8?0	0 243	0.398	18	
			D 15	7 150	6 18	4 86	1 000	0 16,	0 8 0	4	7?
J H	60 M	ASHD	C	6 36	5 66	3 60	0 900	0.29?	0 377	34	
			D 10	6 130	5.24	4 ,0	1 063	0 ?60	0 588	25	172
A. S	50 M	ASHD	C	7 850	7 380	2 72	0 6,0	0 212	0 283	15	
			D 15	8 30	7 410	3 58	0 810	0 212	0 507	11	53
S W	?, M	Cardiomyopathy	C	6 89	6 12	1 68	0 440	0 ?74	0 410	21	
			D 15	6 76	5 89	2 92	0 680	0 212	0 610	15	72
R F	61 M	ASHD	C	5 ??0	5 00	2 80	0 600	0 30?	0 111	30	
			D 15	5 ,80	5 030	3 50	0 700	0 ?86	0 345	21	?2
J F	60 M	Cardiomyopathy	C	6 660	6 ?40	1 92	0 500	0 25	0 ?50	34	
			D 15	6 480	5 7?0	3 160	0 780	0 248	0 4?0	31	96

Mean	*Dd cm*	*Ds cm*	*VPWE cm/sec*	*PWE cm*	*Mean Vcf circ/sec*
C	6 700 ± 0 ?7	6 0?0 ± 0 69	? 860 ± 0 75	0 ?26 ± 0 19	0.39, ± 0 14
D	6 5?0 ± 0 80	,720 ± 0 ,0	4 060 ± 1 0	0 865 ± 0 14	0 537 ± 0 13
		(p < 0 25)	(p < 0 001)	(p < 0 00,)	(p < 0 010)

Dd = end-diastolic diameter Ds = end-systolic diameter PWE = posterior wall excursion dt = duration of contraction VPWE = velocity of posterior wall excursion Vcf = velocity of circumferential fiber shortening = PAWP = pulmonary artery wedge pressure CVP = central venous pressure

63 per cent ($p < 0.005$) Increases in C O and S V were also dose related (Fig 2) C V P monitoring in six patients for a mean duration of 51 hours showed sustained improved levels However digoxin and diuretic agents were added in all patients after the first two hours

Systolic Time Intervals (S T I) Satisfactory recordings were obtained in seven patients There was a mean decrease in Q S I from 563 6 ± 33 6 to 532 9 ± 46 5 (p N S) msec and a mean decrease in LVETI from 402 7 ± 54 4 to 401 0 ± 71 6 (p N S) msec There was a decrease in PEPI from a mean of 160 93 ± 54 9 to 133 1 ± 28 7 msec ($p < 0.05$) The ratio of PEP/LVET decreased from 0 45 ± 0 15 to 0 32 ± 0 13 ($p < 0.01$)

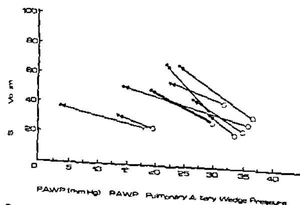


Fig 1 Left ventricular function curves relating stroke volume to P.A W P in eight patients at control *(open circle)* and following dobutamine infusion (10 to 15 µg/Kg/min) *(closed circle)* Thick line represents the average value for all patients

Table II Systolic time intervals

Name	Age & sex	Heart disease	Dose (μg/Kg/min)	H R (beats/min)	BP (mm Hg)	Mean BP (mm Hg)	Q S I (msec)	LVETI' (msec)	PEPI (msec)	PEP LVET	Duration of therapy (hours)
H C	56 M	HCVD	C	112	160/120	133	610.3	475 4	134 9	0 310	
			D 15	100	190/100	137	557 0	427 0	130 0	0 315	44
S H	68 M	ASHD	C	92	120/80	93	515 7	381 4	134 3	0 430	
			D 15	100	130/70	90	534 3	412 9	111 4	0 335	69
S G	53 F	Cardiomyopathy	C	116	110/85	93	513 23	383 0	130 25	0 474	
			D 15	130	110/80	90	543 0	408 5	135 5	0 380	46
J I	34 M	HCVD	C	108	150/130	137	582.8	391 6	191 2	0 700	
			D 15	132	178/130	146	682 2	432 7	149 5	0 400	
R V	34 M	Cardiomyopathy	C	96	110/90	97	569 6	450 2	119 4	0 287	
			D 15	112	108/84	89	524 2	447 4	96 8	0 125	
J H	60 M	ASHD	C	114	130/90	103	570 65	438 8	131 85	0 337	
			D 10	120	150/74	97	562 0	449 7	112 3	0 258	
A S	50 M	ASHD	C	112	100/80	87	–	–	–	–	53
			D 15	100	86/64	71					
H P	61 M	HCVD	C	126	160/100	120	582 9	298 3	284 6	0 650	
			D 10	144	150/90	110	427 6	229 2	198 4	0 540	
S W	25 M	Cardiomyopathy	C	125	110/70	83	–	–	–	–	7[illegible]
			D 15	124	110/80	90					
R F	62 M	ASHD	C	68	120/90	100	–	–	–	–	7[illegible]
			D 15	98	120/90	100					
J E	60 M	Cardiomyopathy	C	108	114/90	100	–	–	–	–	
			D 15	114	120/90	100					

Mean	Q S I (msec)	LVETI (msec)	PEPI (msec)	PEP LVET
C	563 60 ± 33 6	402 7 ± 54 4	160 93 ± 51 91	0 45 ± 0 15
D	532 9 ± 46 5	401 0 ± 71 6	133 4 ± 28 7	0 32 ± 0 13
	p = N S	p = (N S)	p < 0 050	p < 0 01

L V E T I = left ventricular ejection time index P E P I = pre ejection period index Q S I = interval from onset of Q wave on ECG to the A of phonocardiogram (corrected for heart rate) HR = heart rate Other abbreviations as in Table I

was monitored in the ward with a water manometer for a mean duration of 51 hours

Results

The mean hemodynamic S T I and echocardiographic data obtained in the control and steady stage of dobutamine infusion are presented in Tables I to III Ventricular function curve and dose response curves are presented in Figs 1 and 2 Statistical analysis was done using the Student t test

Effect on hemodynamics Systolic blood pressure (BP) increased slightly from a mean of 119 ± 20 to 125 ± 23 mm Hg (p N S) mean diastolic BP decreased from 87 ± 19 to 81 ± 17 (p < 0 05) and the mean BP decreased slightly 97 ± 18 to 95 ± 21 mm Hg (p N S) In one patient (J I) BP increased from 150/130 to 200/130 mm Hg before reaching a steady state at 178/130 mm Hg Another patient increased his BP from 160/120 to 190/100 mm Hg However, in a third hypertensive patient BP decreased from 160/100 to 150/90 mm Hg Systemic vascular resistance decreased from 36 1 ± 0 08 to 19 9 ± 0 6 H R U (p < 0 001) Mean P A P decreased from 42 ± 7 to 36 ± 11 mm Hg (p < 0 02) The pulmonary vascular resistance decreased from 3 80 ± 1 7 to 3 0 ± 1 3 H R U (p N S) The wedge pressure mean decreased 33 per cent (p < 0 001) and R A P decreased 40 per cent (p < 0 005) Heart rate increased from 101 ± 19 to 109 ± 23 (p < 0 05) at infusion rates of 10 to 15 μg/Kg /min of dobutamine A dose-response study in seven patients (Fig 2) demonstrated that increased heart rate was dose related rising from a control of 94 ± 22/min to 97 ± 30/min (5 μg/Kg /min) to 103 ± 32 (10 μg/Kg / min) and 106 ± 29/min (15 μg/Kg /min) The cardiac output (C O) increased 72 per cent (p < 0 001) and stroke volume (S V) increased

mine[1] and acute hypertensive reactions have been observed in some cases treated with dopamine which is structurally closely related to dobutamine[6] The hemodynamic changes in our patients are generally in agreement with those of Akhtar and associates[15]

Echocardiographically Dd did not change but D decreased significantly ($p < 0.025$) reflecting an increase in stroke volume from 30 ± 6 to 49 ± 14 ($p < 0.005$) Other echocardiographic values namely V P W E P W E and mean V C F were significantly altered by dobutamine infusion (Table III) These data confirm previous observations by others that the echocardiogram can detect acute alterations in ventricular functions We did not find echo derived volumes of value perhaps because of the dilated heart in our patients and the small dimensional changes induced by dobutamine The limitations of echocardiographic volumes in measuring acute alterations in ventricular function have been pointed out by Redwood and colleagues

Systolic Time Intervals in our patients revealed a significant decrease in P E P I with insignificant changes in L V E T I and Q S I The ratio of PEP/L VET decreased markedly Thus the influence of dobutamine infusion on S T I is similar to that produced by other catecholamines

Thus in the dose of 5 to 15 μg/Kg /min dobutamine increases the contractility (S T I and echo) and stroke volume (dye–dilution) of the failing heart from a constant end diastolic diameter (Echo) without changing the duration of systole (L V E T) or blood pressure It only slightly increases the heart rate At this dose level it is fairly selectively inotropic to the failing heart

Since myocardial oxygen consumption (MVO) varies directly with heart rate contractile state and systemic arterial pressure the energy cost of this improvement in myocardial function should be less than that caused by inotropic agents that increase heart rate and blood pressure This explains the containment of myocardial infarction size by dobutamine reported by Tuttle and co workers

Our data indicate that in the dose of 5 to 15 μg/Kg /min dobutamine is safe and significantly improves the function of the failing heart It would appear to be a useful drug whenever a potent selective inotropic agent is desired especially in cardiogenic shock Caution should be exercised in its use when moderately severe or severe hypertension exists Further experience and therapeutic trials are needed

Summary

The effects of continuous infusion of dobutamine 5 to 15 μg/Kg /min were studied in 17 patients using right heart catheterizations echocardiography and/or the Systolic Time Intervals HR increase was dose related but insignificant ($p < 0.05$) rate increase was obtained at infusion rates below 15 μg/Kg /min C O increased from 2 9 ± 0 7 to 5 0 ± 1 2 liters/min ($p < 0.001$) and the stroke volume from 30 ± 6 to 49 ± 14 ml / min ($p < 0.005$) The mean BP did not change P A W P decreased from 30 ± 7 to 20 ± 8 mm Hg ($p < 0.001$) and R A P from 20 0 to 12 0 mm Hg ($p < 0.005$) The P E P I decreased from 160 93 ± 54 91 to 133 4 ± 28 7 msec ($p < 0.050$) Echo determined mean VCf increased from 0 387 ± 0 14 to 0 537 ± 0 13 cm ($p < 0.010$) diastolic diameter did not change significantly but the end systolic diameter decreased from 6 020 ± 0 69 to 5 750 ± 0 70 cm ($p < 0.025$)

During a mean infusion period of 75 hours the only side effects noted were transient nausea and/or vomiting at 15 μg/Kg /min dose range in two patients and multifocal P V C s following 68 hours of infusion in another patient It is concluded that in the dose range of 5 to 15 μg/Kg /min dobutamine is well tolerated and is a very potent inotropic agent with only minor effects on the heart rate and blood pressure

We gratefully acknowledge the technical help of Miss Jane Spencer (Echocardiogram) Messrs E L Norwood and L Smith and the secretarial services of Mrs Harriet Ragin and Mrs Patricia Westray Dobutamine was kindly supplied by A F Fasola M D of Eli Lilly Research Laboratories Indianapolis Indiana

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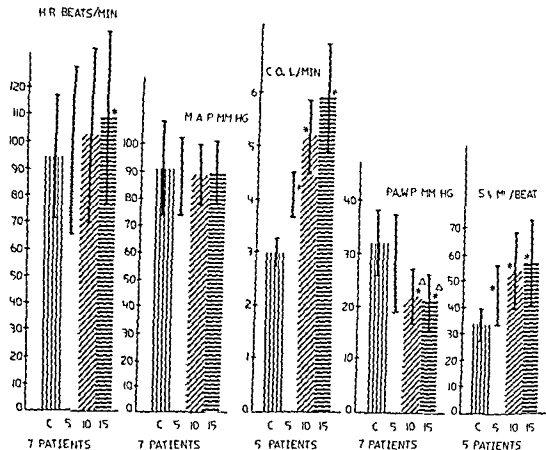


Fig 2 Mean hemodynamic measurements in seven patients (H R M A P P A W P) and in five patients (C O and S V) during control period (vertical bar) infusion of 5 µg/Kg /min (dotted bar) 10 µg/Kg /min (oblique bar) and 15 µg/Kg /min (horizontal bar) Asterisk indicates significant difference from control ($p < 0.05$) triangle indicates significant difference from 5 µg/Kg /min ($p < 0.05$)

Echocardiographic data Two echograms demonstrated significant paradoxical septal motion and were excluded from analysis In two other patients good quality echograms could not be obtained Dd decreased from 6 700 ± 0 77 to 6 57 ± 0 80 cm (p N S) but significant changes occurred in Ds from 6 020 ± 0 69 to 5 72 ± 0 70 cm ($p < 0.025$) Marked changes in V P W E 2 86 ± 0 75 to 4 060 ± 1 00 cm /sec ($p < 0.001$) and in the P W E from 0 726 ± 0 19 to 0 865 ± 0 140 cm ($p < 0.005$) were obtained Mean V C F similarly increased from 0 387 ± 0 14 to 0 537 ± 0 13 cm ($p < 0.010$)

Side effects At infusion rates of 15 µg/Kg / min , two patients (J I) and (H C) with hypertension developed marked elevations in systolic blood pressures and both these patients developed transient nausea and one vomited Dobutamine dosages were reduced to 10 µg/Kg /min One dose of an anti emetic agent was given to the patient who vomited and neither nausea nor vomiting recurred in either patient Antihypertensives which had been stopped 12 hours before dobutamine infusion in both patients were resumed following two hours of acute study, and no further episodes of blood pressure elevations were observed One patient (M N) whose ECG was previously stable following 68 hours of drug infusion developed multifocal P V C s otherwise no significant cardiac arrhythmias were noted No abnormalities of hematopoetic renal or liver functions were observed and no changes in C P K L D H or S G O T occurred during a mean treatment period of 75 hours

Discussion

Our hemodynamic studies showed decreases in P A W P or C V P and increases in cardiac output and stroke volume in all the patients studied Heart rate increase was slight and became significant ($p < 0.05$) only when a 15 µg/Kg /min dose was given Mean arterial pressure generally was unchanged Two patients with moderately severe hypertension showed further systolic blood pressure elevation However a third patient with hypertension did not manifest any increase Acute elevations in systolic blood pressures have been observed previously in 6 patients with systolic pressures greater than 150 mm Hg infused with 8 µg/Kg /min of dobuta

Quantitative study on the size of coronary artery supplying areas postmortem

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Hitherto only few attempts have been made to determine the size and the limits of myocardial supplying areas of single coronary arteries Ahmed and associates examined the hearts of 94 casualties by means of injection and corrosion techniques They estimated the relative amount of myocardium supplied by the right and left coronary artery taking the different thicknesses of the right and left ventricular wall into account The result of the examination was that they found in most human hearts that the myocardium was equally supplied by both coronary arteries Woods determined the part of the myocardium supplied by the right coronary artery by means of angiography as well as by the dissection and weighing of 28 normal and 19 hypertrophied human hearts According to this investigation the right coronary artery supplies 20 to 46 per cent of the left ventricular myocardium in addition to the whole of the right ventricle de Oliveira injected different colored media into the right and left coronary artery After removing the atria and subepicardial fat he weighed the portion of myocardium perfused by the right coronary artery Its size lay between 13 1 and 63 2 per cent (average 38 4 per cent in 32 normal human hearts) and rarely exceeded 50 per cent (four out of 32 hearts) These methods have two disadvantages First the left ventricular myocardium must be dissected into the areas supplied by each coronary artery Second the free part of the right ventricle must be severed from its attachment to the interventricular septum This will complicate histologic and above all topographic studies

Methodical investigations into the size of perfusion areas dependent upon the coronary vascular type are fully lacking Schlesinger has introduced the term of coronary artery preponderance His differentiation of coronary artery patterns into right or left preponderance and balanced circulation was based exclusively on anatomic criteria However it might create the impression of corresponding physiological preponderance of a coronary artery But since the bulk of left ventricular myocardium is so much greater than the bulk of the right myocardium in the majority of all human hearts the left coronary artery is the physiologically preponderant artery[5] However no measurements exist on the size of supplying regions

We have been able to determine the size of supplying areas of the single coronary arteries by using injection and dissection techniques This examination was carried out on normal and diseased human hearts of various coronary vascular types

Material and methods

Altogether 171 human hearts were examined Age distribution is shown in Table I Among the hearts of adults 67 revealed distinct hypertrophy with heart weight of 500 Gm and more In 51 hearts there were old (28) or recent (23) infarctions Ten hearts with recent infarcts showed additional former infarctions scars

The method has been described in detail elsewhere To give a brief outline here the coronary arteries were injected with x ray contrast medium

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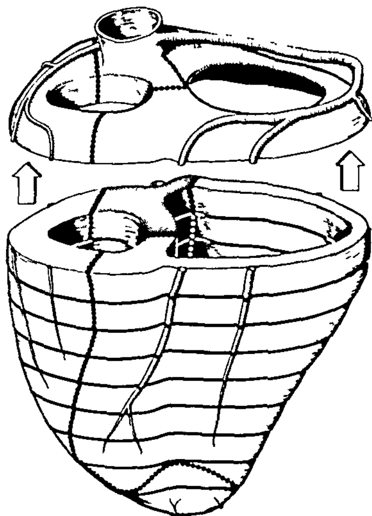


Fig 1 Diagram illustrating the manner in which the hearts were sliced Drawing of the diaphragmatic surface of the heart The basal slice is raised somewhat in order to reveal the vascular areas of the left descending *(cross hatched area)* left circumflex *(stippled area)* and right coronary artery *(linear area)* *The dotted lines on the surface* mark the boundaries between the supplying areas

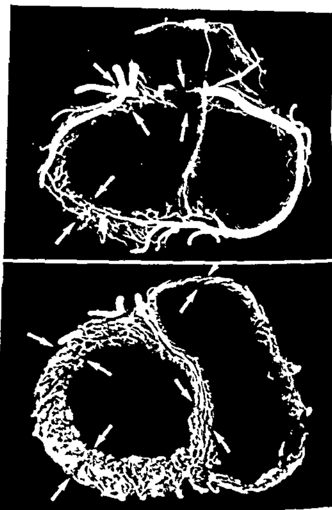


Fig 2 In these radiographs of the basal slice *(upper figure)* and of a slice taken from the middle *(lower figure)* of the same heart (autopsy number S 590/72) the boundaries between the coronary vascular areas are indicated by arrows There is a sharp line of demarcation between the areas Of course one can only determine the vascular areas by comparison with the adjoining slices

Micropaque in 10 per cent gelatine solution under a constant pressure of 100 mm Hg Our usual procedure was not a single coronary injection but the filling of the twofold ligated aorta in order to obtain complete angiographs even in cases of a third coronary ostium After radiography in different planes and formalin fixation the atria were detached from the ventricles at the level of the atrioventricular valve rings The ventricular portion of the hearts was sliced into serial sections 8 mm in thickness parallel to the basis of the heart (Fig 1) Only the first section was frequently somewhat thicker because it enclosed the vascular ring of the right coronary artery and the left circumflex branch Radiographs of the individual sections served as the basis for the evalutation of the coronary supplying areas (Fig 2) The outlines of the myocardium, the free part of the right ventricle and the limits between the supplying areas of the left descending left circumflex and right coronary artery were drawn on contact copies of the ventricular slice roentgenograms

As a rule the borderlines of the vascular supplying areas are easily recognizable if the radiographs of the myocardial sections are systematically analyzed from the base to the apex The partial areas of all slices were measured by a planimeter and the percentage of the coronary supplying areas was calculated with respect to the total myocardial area Moreover the percentage may be expressed in grams of ventricular mass In this way we got the relative part of myocardium perfused by a single coronary vessel The hearts were subdivided into groups according to the coronary vascular type and to pathologic conditions such as hypertrophy or myocardial infarctions

Table I Age frequency of cases studied

Neonates and infants up to the first year	4
1 to 19 years	7
20 to 39 years	12
40 to 59 years	36
60 to 69 years	56
70 to 79 years	46
80 years and older	10
Total	171

Results

A Mean values of all 171 hearts In this study the vascular areas of the three large coronaries (i.e. right coronary artery, left anterior descending and left circumflex branch) were ascertained. The area of the right coronary artery can be defined without difficulty. It covers the part of myocardium supplied by all branches of the right coronary artery. On the other hand, the delimitation of the vascular regions of the two left coronary arteries is more problematic if there is an additional branch arising in the bifurcation of the left coronary stem. This is referred to in various ways, for instance *ramus medianus*,[2] *ramus obliquus*[13] or *ramus diagonalis*.[1] Brink[12] used the term "third primary division" of the left coronary artery and Hoffmann and associates[8] used the term "Trifurkationstyp." We found such a trifurcation in 55 per cent of the hearts under study and even a multiple division of the left coronary trunk in 4.7 per cent. We always added the vascular area of the tripus branch to the area of the left anterior descending artery.

On the average, the left coronary artery of all hearts examined supplied just under two thirds of the entire ventricular myocardium—63.8 per cent—while slightly over one third is supplied by the right coronary artery—36.2 per cent. The anterior descending branch is responsible for the greater part of the supplying area of the left coronary artery. It supplied on average 41.5 per cent of the entire ventricular myocardium.

The musculature of the left ventricle, consisting of the free left chamber wall and the whole interventricular septum, was supplied on the average of 79 per cent by the left coronary artery. About two thirds of this came from the anterior descending branch. Twenty one per cent of the left ventricular myocardium was supplied by the right coronary artery.

B The sizes of supplying areas dependent upon coronary vascular types We defined the

Table II Size of the supplying areas as a percentage of the whole ventricular myocardium related to the coronary vascular types

Coronary vascular type	No	Per cent supplied myocardium: R	La l	Lc
Left coronary artery type	19	16.4	43.8	39.8
Normal coronary artery type	129	37.3	41.7	21.0
Right coronary artery type	23	46.4	39.0	14.6

Abbreviations: R = right coronary artery; Lad = left descending coronary artery; Lc = left circumflex coronary artery.

coronary vascular types as follows:[7]

Left coronary artery type The *ramus descendens posterior* stems from the left circumflex branch and the latter may even transverse the posterior interventricular sulcus and terminate at the posterior wall of the right ventricle.

Right coronary artery type The right coronary artery ends at the *margo obtusus* or may reach the left anterior wall.

Normal coronary artery type All the remaining hearts, which represent the majority, rank among normal types. In these the left posterior ventricular wall is supplied by both the right and left branches.

The mean values for the different coronary vascular types among all 171 hearts are shown in Table II.

The percentage of myocardium supplied by the left anterior descending branch varied only slightly. In left coronary artery types it was on the average slightly larger, in right types slightly smaller than in normal types. Considerable variations emerged, however, in the sizes of supplying areas of the right and left circumflex coronary artery (Fig. 3). They revealed a reciprocal ratio. In hearts of right coronary type the perfusion area of the right coronary artery is large, that of the left circumflex branch small. In these hearts the right coronary artery supplied slightly less than half of the whole ventricular myocardium. In the hearts of the left coronary type, the vascular area of the left circumflex branch is large, covering on the average 40 per cent of the entire ventricular musculature. That of the right coronary artery, on the other hand, is small. The further subdivision of normal coronary types is possible depending on the boundaries on the left posterior wall.[11] The size of the supplying areas in subtypes is shown in Table III. As expected, the

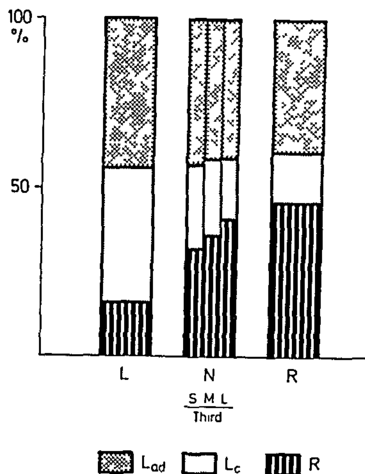


Fig 3 Summary of results Size of supplying areas (expressed as a percentage of the entire ventricular myocardium) of left descending (L_{ad}) left circumflex (L_c) and right coronary artery (R) in each of the coronary artery types L = left type N = normal type R = right type The normal type is subdivided according to the boundaries between the right and left circumflex branch in the septal (S) medial (M) or lateral (L) third of the posterior left ventricular wall

supplying area of the right coronary artery increases as it extends over the posterior left wall to the left side wall At the same time the supplying area of the left circumflex branch diminishes accordingly

C Hearts with right preponderant coronary artery In our study material the left coronary artery with its branches generally supplied a greater part of the myocardium with blood than the right coronary artery This included the hearts of the right coronary vascular type hearts of neonates with their physiological right ventricular hypertrophy and adult hearts with right ventricular hypertrophy Of the hearts studied there were only nine in which more than half of the ventricular myocardium was supplied by the right coronary artery In six of these nine hearts a right coronary type existed four of which were combined with right ventricular hypertrophy The remaining three hearts were of the normal

Table III Size of the supplying areas of subtypes of normal coronary type Position of the boundary between the right and left circumflex coronary artery in the septal, medial and lateral third of the posterior left ventricular wall

Coronary vascular type	*No*	*Per cent supplied myocardium*		
		R	*Lad*	*Lc*
Septal	25	31 8	43 0	2[illegible]
Medial	55	36 5	41 5	2[illegible]0
Lateral	49	41 1	41 0	1[illegible]9

Table IV Size of the supplying areas related to left or right ventricular hypertrophy

A Hearts with unilateral or prevailing left hypertrophy

Weight (Gm)	*N*	*Per cent of free part of right ventricular wall*	*Per cent of supplied myocardium*		
			R	*Lad*	*Lc*
603	22	17 6	34 8	43 [illegible]	[illegible]20

B Hearts with unilateral or prevailing right hypertrophy

Weight (Gm)	*N*	*Per cent of free part of right ventricular wall*	*Per cent of supplied myocardium*		
			R	*Lad*	*Lc*
577	16	33 0	44 1	40 4	15 5

See Table II for abbreviations

type, but with a hypoplastic left circumflex branch It did in fact reach the left posterior wall at the basis of the heart but barely descended so that the bulk of the left posterior ventricular wall was perfused solely by branches of the right coronary artery Moreover all three hearts showed a distinct right ventricular hypertrophy In our test material the highest figure for the vascular area of the right coronary artery—57 8 per cent—was encountered in a heart with a marked eccentric right and left ventricular hypertrophy in primary cardiomyopathy with hypoplasia of the left circumflex branch

D Hearts with right or left hypertrophy Altogether our observation material included 38 hearts of the normal vascular type with unilateral or prevailing hypertrophy of one cham

ber A relative weight portion of the free right chamber wall of more than 26 per cent served as the criterion for distinct right ventricular hyper trophy Less than 20 per cent served as the criterion for left ventricular hypertrophy Table IV shows the sizes of supplying areas in hearts with left or right ventricular hypertrophy

The supplying area of the right coronary artery in cases of right hypertrophy is on the average larger than in cases of left hypertrophy These differences are significant for the right coronary artery In hearts with bilateral hypertrophy including hearts with old or recent infarctions we observed no significant differences in the size of coronary supplying areas between the individual coronary vascular types

Discussion

The method employed in this study to deter mine the size of coronary supplying areas presup poses a successful coronary angiography It is sometimes difficult to determine the boundaries of vascular regions if they appear flat due to highly developed collateral vessels The simple serial cross sectioning of the ventricles has the advantage of permitting the preparation of paraffin large sections through the entire right and left ventricular myocardium The method is not without possible sources of error The possi bility of error lies chiefly in the various thick nesses of the myocardial slices An electric slicer helps to obtain fairly uniform thickness of the serial sections Sometimes however there are deviations in the thickness of the first manually dissected basal slice and also in the last remaining apical slice These are of course very small Yet control examinations of ten hearts revealed only slight consequences of these inaccuracies on the relative size of the coronary supplying areas Of course one has to realize that the results are a reasonable approximation of the real values A comparison of planimetrically determined values and those values obtained by additional weighing shows on the average merely the following differ ences

Right coronary artery 0 85 per cent (0 02 to 1 67 per cent)

Left anterior descending branch 1 02 per cent (0 26 to 2 27 per cent)

Left circumflex branch 0 25 per cent (0 01 to 0 70 per cent)

The present study shows that the left coronary artery with its anterior descending and circumflex branches perfused in almost every case the major portion of ventricular myocardium This ac counts for the larger mass of the left ventricular musculature The right coronary artery is as a rule very long and its vascular area on the cardiac surface is correspondingly large But this vessel mainly supplies the thin walled right ventricle and only parts of the posterior ventricular septum and posterior left ventricular wall The sizes of supplying areas vary above all according to the different coronary vascular types First and fore most the area of the right and left circumflex coronary artery is affected [7, 1] In so far as the long right coronary artery corresponds with a short left circumflex branch and vice versa the supplying areas of these vessels are in an inverse ratio to each other The same applies to the reciprocal length the size of the supplying area of the posterior descending branch and the anterior descending left coronary artery

Contrary to the supplying area of the right and left circumflex coronary artery that of the ante rior descending left branch is almost constant even in different coronary vascular types It was noted that the average values for the vascular area of this vessel in the normal vascular type lie slightly above those of the right coronary type In the left coronary type the increase is more obvious The explanation for this tendency could be that the left anterior descending branch in right coronary types scarcely ascends into the posterior interventricular groove having run round the cardiac apex In normal or left coro nary types it frequently supplies the entire cardiac apical region ascending to various degrees into the posterior sulcus [9]

A marked cardiac right or left hypertrophy is usually of less importance to the size of the coronary supplying area than is an extreme coronary vascular type There must be a unilateral hypertrophy to a high degree before the size of the coronary supplying area is affected

Our study group has determined that the diam eters of coronary vessels without or with only slight sclerotic lesions give an approximate indi cation of the size of the supplying areas Coronary arterial lumens have been seen to correlate best with the size of supplying areas in accordance with earlier investigations [6]

The sizes of supplying areas are not only of anatomical interest Under pathologic conditions

it is, for example of importance if parts of the conducting system are involved by pathologic changes in the supplying branch The A V node artery in hearts of the normal or right coronary vascular type stems from the right coronary artery, but in the left coronary type, usually from *the left circumflex branch*

In infarcted hearts the consequences for hemo dynamics will be more pronounced the more extensive the vascular supplying area beyond the occlusion is Beyond that, the determination of the boundaries of the supplying areas presents the opportunity to analyze topographic relations between ischemic myocardial changes and the supplied area of one single coronary artery branch behind a stenosis or an occlusion

Summary

The relative amount of myocardium perfused by the three large coronary arteries was deter mined in 171 human hearts postmortem Roent genograms of transverse serial sections of the ventricular myocardium enabled planimetrical measurements With little variation, an average of 41 5 per cent of the entire ventricular myocar dium was supplied by the left descending coro nary artery Both left branches supplied an average of 63 8 per cent and the right coronary artery supplied 36 2 per cent of the myocardium The size of supplying areas in particular that of the right coronary artery and the left circumflex branch, *was mainly dependent upon the coronary* artery types As a rule cardiac hypertrophy did not influence the size of coronary supplying areas as much as did the coronary artery types Only very few hearts revealed that the myocardium was supplied to a greater extent by the right coronary artery than by the left (5 3 per cent) There is a close relationship between the size of the myocardial supplying area and the lumen of the corresponding coronary artery

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Large flabby hearts in hypertension

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The high frequency of large flabby hearts among patients dying with hypertension in Ibadan has impressed the authors and it has been decided to study this problem As these hearts appear to correspond to the usual descriptions of idiopathic cardiomegaly or idiopathic cardiomyopathy or Nigerian heart muscle disease the problem has been that of separating the dilated hypertensive hearts from these The predominant feature is dilatation of the left ventricle There is usually accompanying right ventricular dilatation or dilatation of all chambers resulting in a globular appearance Left ventricular hypertrophy is frequently present The myocardium is soft flabby usually pale and the trabeculae and papillary muscles are flattened Foci of mild or moderate endocardial fibrosis may be present with other phenomena for example mural thrombosis

The authors impressed with the numbers of such hearts among patients dying with hypertension undertook a systematic study of this problem to determine the true frequency of such hearts among hypertensive patients at autopsy to ascertain what varieties there were and to uncover what factors might be responsible for the development of these features and what differences there might be between these hearts and true idiopathic cardiomegaly

In Ibadan the condition called heart muscle disease used to account for 15 per cent of adult hospital admissions according to Brockington This percentage has decreased in recent years with the increasing acceptance of more careful criteria in the diagnosis of hypertension and perhaps greater awareness of rheumatic heart disease Currently the clinical diagnosis is made at death on approximately 10 to 15 autopsied patients per year Among these autopsy studies would accept one to three cases a year and even these are subject to review

It seemed to the authors that definitions of hypertension and cardiomegaly were essential for this work and a selection of only adult patients with hypertension and cardiomegaly for study would leave little room for error No regard is given in this study to the clinical diagnosis of hypertension or of the heart condition or to the cause of death

Materials and methods

Only autopsied hypertensive patients aged 15 years and above who had cardiomegaly were included in this study All such male patients who were autopsied in the years 1971 and 1972 were studied and female patients from 1970 to 1972 in order to have comparable numbers For the purpose of this study hypertension was defined by diastolic pressure of 90 mm Hg and above in the male and 80 mm Hg and above in the female Since the average normal adult Nigerian heart weight is about 280 Gm cardiac weight above 305 Gm was taken as abnormal in this study

The data for both sexes were separately recorded All the hearts were available and were examined by the authors to determine abnormalities These were separated into three types—the classical concentric or selective left ventricular hypertrophy of hypertensive heart disease large flabby hearts and hearts with intermediate configuration The hearts classed as large flabby hearts had left ventricular dilatation as a constant feature In many there was also dilata

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Table I Appearance of hearts at autopsy Hypertensive patients

	Large flabby hearts	*Selective L V hypertrophy*	*Intermediate configuration*	*Total*
Male	18	15	5	38
Female	18	18	5	41

Table II Hematocrit of 39 patients whose reports were available

Male		*Female*		
Hematocrit		Hematocrit		
40% or above	3	35% or above	3	
25% to 39%	10	25% to 34%	4	
Less than 25%	10	Less than 25%	9	
Total	23		16	
Total male and female				39

tion of the right ventricle or of all cardiac chambers Varying degrees of left ventricular hypertrophy were present in many but dilatation predominated Left ventricular thickness was recorded Those classified as intermediate configuration were clearly hypertensive hearts with selective left ventricular hypertrophy but in which dilatation was considerable the dilatation being biventricular in most cases and involving all chambers in some All hearts with other identifiable disease e g rheumatic heart disease or endomyocardial fibrosis were excluded from the study The large flabby hearts were examined histologically The hematocrit was recorded in all cases in which the test results were available Records of kidney weights and gross appearances were reviewed and the kidneys which were in the normal weight range were subjected to histologic examination

Results

There were 38 males and 41 females in the study the age range in both sexes being 15 to 70 years

Blood pressure The blood pressure among the males ranged from 150/90 through 280/160 to 220/180 mm Hg Among the females the range was 120/80 through 240/160 to 290/210 mm Hg

Hearts The classification of cardiac configuration is shown in Table I At least as many hearts as showed typical hypertensive concentric left

Table III Hematocrit of 21 patients with large flabby hearts

		Male	*Female*	
Hematocrit	30% or above	4	0	
	Below 30%	9	8	
Total		13	8	
Total male and female				1

ventricular hypertrophy displayed a dilated or globular, flabby appearance The large flabby hearts weighed 310 to 585 Gm among the men and this was the same weight range as the hearts showing concentric left ventricular hypertrophy apart from an exceptionally large flabby heart which weighed 815 Gm Among the females the weight range was also comparable between the dilated hearts and those with concentric left ventricular hypertrophy 305 to 505 Gm one large flabby heart weighing 560 Gm Left ventricular thickness of the dilated hearts varied from 1 4 to 2 3 cm among the men and 1 4 to 2 2 cm among the women The endocardium of about two thirds of these hearts showed focal opacifications of mild fibrosis usually in the left ventricle and occasionally in the right ventricle Endocardial fibrosis was moderate in only a few cases Left ventricular mural thrombosis was present in a few hearts The coronary arteries were free of atheroma except in a few elderly patients and diabetics in which there were mild patchy lesions

Hematocrit Records of the hematocrit were available in 23 males and in 16 females (Table II) Among the 23 males only three had hematocrit of 40 per cent or above In 10 patients the hematocrit was less than 25 per cent Among the 16 females only three had hematocrit of 35 per cent or above In nine cases the hematocrit was less than 25 per cent

Among the males with flabby hearts the hematocrit was known in 13 cases In nine of the e it was below 30 per cent In all eight females with flabby hearts whose hematocrit was known it was below 30 per cent (Table III)

Kidneys The kidneys were grossly abnormal in 72 of these patients 65 being contracted and granular or scarred and seven enlarged kidneys of cystic disease hydronephrosis and compensatory hypertrophy following previous nephrectomy The seven kidneys with weights within normal range were all microscopically abnormal with

features ranging from rapidly progressive glomerulonephritis infarcts and chronic pyelonephritis Not a single kidney was normal Fig 1 demonstrates contracted granular kidneys with a large flabby heart from the same patient

Histology of the flabby hearts The 36 dilated hearts were subjected to histologic examination Sections of left ventricle were available in each case Myocardial hypertrophy was a prominent feature in 13 hearts patchy fibrosis was present in three and myocytolysis in two The myocardial fibers were disposed in an orderly arrangement and in a fair number of the hearts there were zones of irregularities of shape and size of myocardial nuclei this feature showing no particular association It was present in the two hearts which manifested myocytolysis but was not more prominent in these than in some of the other hearts Other degenerative alterations e g myocardial basophilic degeneration were not a feature In no case was there evidence of myocarditis vasculitis or myocardial infarction Hypertrophy of mild or moderate degree was present in the majority of the hearts Left ventricular mural thrombosis with organization was demonstrated in several hearts including one with myocytolysis In these cases there was subjacent endothelial lymphocytic reaction Foci of interstitial edema were present in some of the hearts The endocardium of some hearts showed patchy mild fibrosis more commonly in the left ventricle than in the right In only a few cases were some of the fibrous patches of moderate thickness sending septa into subendocardial myocardium Mural thrombi were not always related to endocardial fibrosis The coronary arteries were free of atheroma except for minor inconspicuous lesions in a few elderly patients and diabetic patients

Discussion

The view that idiopathic cardiomegaly or congestive cardiomyopathy (Nigerian heart muscle disease) might be a manifestation of hypertensive heart disease has been expressed by previous authors in recent years As the diagnosis of idiopathic cardiomegaly is one of exclusion in the clinical situation and the features on electrographic radiologic and other investigations are nonspecific autopsy provides the best means of arriving at such a diagnosis The inconclusive nonspecific result of sophisticated pathologic investigations including electron microscopy and



Fig. 1 Specimen photograph of a large flabby heart and contracted granular end stage kidneys from a hypertensive patient

histochemistry in this condition has been commented upon The diagnosis is based on the presence of marked left ventricular or multichamber dilatation in a heart which has no other abnormalities to explain the dilatation The problem which has not been solved with this descriptive diagnosis is whether or not factors extrinsic to the heart or even intrinsic factors which are not easily identified could produce identical cardiac dilatation and the other alterations In particular could systemic hypertension in some cases in cardiac failure with decrease in stroke output followed by normotension eventuate in marked left ventricular dilatation? Oakley described a total of 14 patients among her 80 patients with congestive cardiomyopathy who had sustained hypertension after recovery from prolonged left ventricular failure with normotension Brockington and colleagues in a debate on the relevance of hypertensive heart disease in congestive cardiomyopathy stated that 70 per cent of the patients he saw in Ibadan with Nigerian heart muscle disease had raised blood pressure which responded readily to therapy

The definition of hypertension as a diastolic

pressure of 90 mm Hg and above among men and 80 mm Hg and above among women is based on our experience in Ibadan The fact that patients in this study whose diastolic pressures were never recorded above these levels had severe chronic renal disease and cardiomegaly bears out the sinister significance of these levels of blood pressure in Nigerians The lack of definition of hypertension may in part be responsible for the failure to recognize it in patients some of whom might already have enlarged hearts which are then labelled as heart muscle disease' or idiopathic cardiomyopathy The presence of a diastolic pressure of 80 mm Hg in a woman in whom renal impairment is found on investigation should be regarded as confirmatory of hypertension The presence of cardiomegaly in such a patient must be regarded as hypertensive heart disease if investigations exclude such other cardiac conditions as valvular and ischemic heart disease and endomyocardial fibrosis

In reviewing the literature and standard texts on idiopathic cardiomegaly it is apparent that even when raised blood pressure has been recognized it is frequently not taken into account in assessing the etiology of the cardiomegaly[1,4] Probably because of the ready response of the hypertension to treatment in these patients[1] the hypertension is quickly forgotten and is regarded as not having been of significance in the patient Brockington and Edington recognized this problem of low hypertensive levels of blood pressure in patients dying with otherwise unexplained myocardial failure (labelled heart muscle disease) in a review of adult heart disease in Ibadan Their autopsy study was based on a review of protocols Authors generally do not state what levels of blood pressure they regard as normal when the raised pressure is said to have responded to treatment It is possible that a diastolic pressure of 80 mm Hg in a female is regarded by these authors as not hypertensive Also in Ibadan it is common to discuss reactive hypertension a term implying that when some patients go into left ventricular failure they develop systemic hypertension This concept has been challenged by Brockington and the phenomenon probably cannot occur On the contrary normotension may develop in cardiac failure in a hypertensive patient due to decreased stroke volume and velocity of ejection[1] Brockington and Edington have presented a typical case of a 45 year old hypertensive man with presenting blood pressure of 180/130 This patient defaulted periodically and reappeared in cardiac failure with decreasing blood pressure, the terminal admission B P being 110/90

In this study, the numbers of hearts of hypertensive patients at autopsy which display left ventricular or multichamber dilatation as their principal feature are approximately equal to the numbers with concentric or selective left ventricular hypertrophy The dilated hearts have the same configurations and histologic features as those of idiopathic cardiomegaly, and indeed several of these hearts had been so diagnosed at autopsy The mechanism for concentric left ventricular hypertrophy in systemic hypertension is hemodynamic The degree of hypertrophy depends on time and the level of increase of peripheral resistance which is reflected in the diastolic pressure When these hearts go into failure, as long as the myocardium remains intrinsically healthy, the response to treatment is excellent The response of patients with so called idiopathic cardiomegaly is comparable to this[1] If these patients in fact had intrinsic heart muscle disease, such good response to treatment could not occur It seems that these are hearts of hypertensive patients with healthy muscles which have undergone left ventricular or generalized dilatation rather than concentric left ventricular hypertrophy

What factors are responsible for failure of selective left ventricular hypertrophy to develop and for the development instead of marked left ventricular dilatation? Hypertrophy is present in the majority of these hearts in our experience It has been judged by Oakley[3] to be an expression both of the severity of functional impairment (left ventricular failure) and its duration It is likely that the hypertrophy is also an expression of the antecedent hypertension or concurrent persistent low hypertensive levels of blood pressure Left ventricular thickness determined in the present study varies in the dilated hearts from 1 4 to 2 3 cm The upper ranges are comparable to the left ventricular thickness of the hearts manifesting concentric left ventricular hypertrophy However thickening of the left ventricular wall in these hearts is overshadowed by the much more considerable dilatation of the chamber Another notable feature among the dilated hearts is the flattening of the trabeculae carneae and even of

papillary muscles in contrast to the prominent projecting trabeculae of concentric or selective left ventricular hypertrophy

On review then all patients in this study have hypertension and cardiomegaly by selection and chronic renal disease on pathologic examination But whereas some of the hearts display concentric or selective left ventricular hypertrophy typical of hypertension approximately an equal number show striking left ventricular or generalized dilatation with flattening of the trabeculae carneae and varying degrees of hypertrophy It was decided not to compare heart weights with the degree of hypertension in view of the variable factors involved e g duration of hypertension varying levels of blood pressure maintenance of therapy frequency and duration of cardiac failure which cannot be taken into account in this study but which might affect heart weight However it can be hypothesized that patients whose blood pressures were in the low hypertensive ranges might over a period develop left ventricular hypertrophy which might not be of comparable thickness to those with blood pressure in high hypertensive ranges If these hearts go into failure dilatation is likely to be a more marked feature than concentric thickening

Factors which are likely to precipitate cardiac failure in patients whose blood pressures are in the low hypertensive ranges are to be sought One such possible factor is anemia In the present group of patients with dilated hearts serious anemia with hematocrit below 30 per cent was present in all the female patients and in nine out of 13 patients whose hematocrit was known The importance of anemia in the development of unexplained myocardial failure has been pointed out by Brockington and Edington They gave an average presenting hemoglobin of 7 6 Gm per 100 ml of blood among their patients with cardio renal failure The present study suggests that anemia with hemoglobin levels above this is important especially in combination with hypertension It is unfortunate that when anemic heart disease has been mentioned or discussed by several previous authors no definition has been given of what levels of hemoglobin or hematocrit constitutes anemia It is indeed surprising the large numbers of anemic African patients that are seen by doctors daily without the diagnosis of anemia being made The present authors are satisfied that the normal hemoglobin levels of healthy Nigerians of high economic classes are the same as those of North Americans and Europeans The fact that a large proportion of the population in the lower economic classes have low hemoglobin or hematocrit levels only indicates the large proportion of the population that is anemic The anemia takes its toll in general well being and productivity and affects internal organs the heart perhaps being principally affected In this study the clinical diagnosis of anemia had been made in only those patients with very low hematocrit value mostly below 25 per cent In the other patients who were also significantly anemic the importance of the anemia in contributing to the cardiac condition was largely not taken into consideration

Knight[9] has discussed the hemodynamic factors of anemia in heart disease In this article he also points out that figures quoted for anemia as cause of heart failure are usually underestimates The paper by Williams and colleagues also shows a difference between clinical and autopsy assessment of the significance of anemia in heart disease Anemia is stated to be the cause of clinical heart failure in 2 4 per cent of cases while their necropsy series shows that 5 2 per cent of cardiac deaths were due to anemia In the present study anemia is defined by hematocrit below 40 per cent in males and below 35 per cent in females The great majority of these patients were anemic Even taking a hematocrit level of 30 per cent a level at which there could not be many objections to the diagnosis of anemia again a great majority of the patients with dilated hearts in hypertension were anemic below this level The combination of increased peripheral resistance and increased work load due to anemic hypervolemia probably make such demands on the myocardium as the anoxemic blood is not able to cope with Such a heart may consequently tend to fail early in the course of hypertension or at relatively low hypertensive levels of blood pressure Myocardial hypertrophy might therefore not develop to the classical concentric degree Instead left ventricular failure is marked by dilatation

The pathology of these dilated hearts is in no way different from that of classically described heart muscle disease or idiopathic cardiomyopathy The heavier hearts with thickened left ventricular wall most closely resemble the clas

sical descriptions However, there is a range of left ventricular wall thickness in idiopathic cardio myopathy (congestive cardiomyopathy[10]), and most of the dilated hearts in the present study would be acceptable as cases of idiopathic cardiomegaly judging by pathologic features Different features on microscopic examination of idiopathic cardiomegaly are variously emphasized by different authors For example basophilic degeneration in myocardial fibers which is emphasized by McKinney,[11] is not usually seen in Ibadan[1] In the experience of one of the present authors (Ed B A) this alteration is more frequently encountered in elderly North American and English Caucasians than in Nigerians, and has been described in other conditions[11] Myocytolysis originally described by Smith[14] in coronary heart disease, and later by Schlesinger and Reiner[4] has been detailed by Edington and Gilles[4] in idiopathic cardiomyopathy In Nigerian patients in whom coronary atherosclerosis is rare currently myocytolysis has most frequently been encountered in heart muscle disease (idiopathic cardiomegaly) and endomyocardial fibrosis Some authors make no mention of this feature in their descriptions of the histology of idiopathic cardiomegaly[11] Myocytolysis was encountered in two hearts in this study along with other features usually described in idiopathic cardiomegaly These two hearts had all the usual characteristics of classical heart muscle disease as seen in Ibadan However, they do not stand out differently from the other hearts in this study except in the presence of myocytolysis and the fact that the 560 Gm heart was the heaviest heart among the women Many hearts of the males were heavier than this and showed no myocytolysis

It seems quite impossible to find criteria which will separate these dilated hearts from those of so called heart muscle disease or idiopathic cardiomegaly These hearts show the same type of changes Several of these hearts had at the time of autopsy been given that diagnosis (i e heart muscle disease or idiopathic cardiomegaly) The authors are currently assessing the clinical significance of anemia in heart disease in Nigerians and are presently initiating experiments to produce comparable cardiac lesions in animals, employing a combination of anemia and hypertension These large flabby hearts in hypertensive disease should be referred to simply as dilated hearts in hypertension This is likely to drastically reduce the numbers of so called 'idiopathic cardiomegaly and avoid the use of such terms as 'congestive cardiomyopathy'[10] for which there is little justification, and of heart muscle disease, since the myocardium of these patients is essentially undamaged as evidenced by prompt response to treatment

Summary

Examination of 79 enlarged hearts of autopsied adult hypertensive Nigerian patients shows that dilated, globular flabby hearts indistinguishable from so called "idiopathic cardiomegaly (heart muscle disease) are as frequent as classical concentric or selective left ventricular hypertrophy Several of these dilated hearts had previously been diagnosed as idiopathic cardiomegaly at autopsy The great majority of these patients had significant anemia which was probably contributory to early cardiac failure, marked left ventricular or generalized dilatation and varying degrees of thwarting of the myocardial thickening process The myocardium however, remains essentially undamaged and will readily respond to treatment These hearts show the same type of change as hearts which have variously been labelled idiopathic cardiomegaly, heart muscle disease congestive cardiomyopathy' etc It should be realized that diastolic blood pressure of 90 mm Hg and 80 mm Hg in the African male and female respectively probably indicate established hypertension and that hemoglobin levels which constitute anemia in the western world constitute anemia in the African and will have its effects on the organs including the heart A combination of anemia and relatively low hypertensive levels of blood pressure is likely to affect the heart Consideration of these two factors will probably reduce the numbers of cases diagnosed as idiopathic cardiomegaly It is suggested that these large flabby hearts in the presence of raised blood pressure be simply referred to as dilated hearts in hypertension

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Correlation of age and heart weight with tortuosity and caliber of normal human coronary arteries

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Almost 30 years ago Harrison and Wood[1] observed that the size of the coronary arteries varies directly with the heart weight in both normal and hypertrophied hearts irrespective of the cause of hypertrophy "[1] Their conclusion contradicted other studies of the day, one of which stated that coronary arteries increased in size only in hearts weighing up to 500 Gm but not in heavier hearts Subsequent studies by other investigators have continued to support both notions Some suggest that with hypertrophy the myocardium can outstrip its blood supply and that this failure of the epicardial coronary arteries to keep pace' with the enlarging myocardium can lead to myocardial infarction, ischemic injury and/or heart failure [1,3] Other studies have observed a proportional increase in coronary size with myocardial mass and have generally described a linear relationship of heart weight with cross sectional area [4-6]

In a recent study [7] we demonstrated that measurements of coronary artery parent and branch vessel diameter (D) at a branch point corresponded closely to the formula

$$(D_{Parent})^3 \approx (D_{Branch_1})^3 + (D_{Branch_2})^3$$

This equation had been theoretically predicted from an application of the principle of minimum work as being that relationship of calibers which allows blood to flow in the most efficient manner [8,9] If the relationship holds true for the circulation in general, then the coronary artery diameters cubed should be proportional to heart weight in order to maintain a consistent volume of blood flow per gram of tissue in the growing o pathologically enlarged heart Theoretically, then, a rather small increase in epicardial coronary artery caliber should provide adequate and efficient blood flow for even very large hearts

An age related dilatation with accompanying tortuosity due to lengthening is recognized in the aorta and other large elastic arteries[1] and has been ascribed to a relative loss of elastic and increase of collagenous structural elements However dilatation of the coronary arteries as a simple function of age has not been found [4,5] Although commented upon [11] tortuosity of the coronary arterial tree does not appear to have been specifically investigated The increased vessel length which produces tortuosity could be expected to increase resistance to blood flow and also increase the complexity of flow patterns within the lumen

In the present study data from a large series of hearts with angiographically normal coronary arteries were analyzed Relationships between heart weight coronary artery caliber and tortuosity presence and type of cardiac disease and the age of the patients were examined An attempt was made to determine which factors influenced coronary artery caliber The range of occurrence and the significance of coronary artery tortuosity were also investigated

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Materials and methods

The hearts from 738 patients in the autopsy files of The Johns Hopkins Hospital studied by a standard method employing coronary arteriography and fixation in distention [2] were reviewed The coronary artery injection procedure involves the use of a barium-pigment-gelatin mass which is prepared in the same way for each specimen and injected under similar manometer pressures of 100 to 150 mm Hg It has been shown that the method distends vessels to diameters closely approximating those found in life Two sets of stereoscopic radiographs one made on the intact heart and one of the transverse sections of the heart were examined to assess the adequacy of the arteriographic injection procedure Radiographs of specimens with adequate filling of both right and left coronary arterial trees were graded on a scale of 0 to 4+ for severity of coronary artery disease The diameters of the right left left anterior descending and circumflex coronary arteries were measured directly on the radiographs using a scale and hand lens When the left coronary artery had additional branches these were also measured Left main coronary artery could not be measured in many hearts because of distortion or non filling of that vessel from ligature placement during the injection procedure No compensation was made for the trivial magnification effects caused by the divergent x ray beam

The fresh heart weight ventricular volumes patient s age and the character of any cardiac disease was determined from information previously recorded during study of the case The left ventricular surface area was calculated from measurements of ventricular length and diameter by considering the ventricle to be a prolate hemispheroid [3] The patient s body surface area was determined from a nomogram which relates body length and weight to surface area

A tortuosity index for the coronary arteries was calculated The actual length of a segment of left anterior descending coronary artery in the anterior interventricular groove from its origin to the heart border as seen on the radiograph was measured along its curvature with a device designed to measure distances on maps The straight line distance between the beginning and ending points of the artery segment measured was determined and divided into the actual artery length to yield the tortuosity index Independent of this tortuosity index a qualitative grading system for tortuosity was devised in which 2+ was normal tortuosity 0 1+ were grades of straightening and 3+ and 4+ represented grades of increased tortuosity It is of note that no vessels of 0 tortuosity were observed

A diameter for a theoretical single coronary artery (D_T) supplying blood to that heart was calculated from the diameter of the right (D_R) and left (D_L) coronary arteries by the formula

$$(D_{Th})^3 = (D_R) + (D_L)^3$$

For those hearts in which the left main coronary artery could not be measured directly it was calculated from the measured sizes of the branches into which it directly divided usually a left anterior descending (LAD) and circumflex (CIRC) branch and sometimes diagonal (DIAG) branches also by the formula

$$(D_L) = (D_{LAD})^3 + (D_{CIRC}) + (D_{DIAG})$$

The validity of this formula for determining the relationship between parent and branch vessel caliber has been presented in an earlier study

Each heart was assigned to one of four disease groups on the basis of a previous review of the clinical and pathological features of the case Normals were those cases with no evidence of heart disease LVH was predominant left ventricular hypertrophy secondary to resistance to outflow as seen for example with systemic hypertension or aortic stenosis RVH was predominant right ventricular hypertrophy as seen for example secondary to mitral stenosis or pulmonary disease Myocardiopathy was defined as those cases with left ventricular hypertrophy and dilatation of the chamber Causes of left ventricular dilatation included aortic or mitral regurgitation or previous diffuse myocarditis The hearts which showed features of more than one of the abnormal states were placed in a category according to the dominant or primary alteration

Relationships were sought through correlation matrices between patient s age heart weight (D_{Th}) and the sum of (D_R) and (D_L) when n was set equal to 1 2 3 and 4 tortuosity tortuosity index ventricular volumes left ventricular length and surface area grams of heart per square meter body surface area the disease group and the logarithms of the numerical values Graphic and statistical methods were employed The facilities of The Johns Hopkins University Computer Center were used to carry

Table I Characteristics of disease groups

Group	Number	*Age (years)* *Mean ± SD* *(range)*	*Heart weight (Gm)* *Mean ± SD* *(range)*	*D_{Th} (mm)* *Mean ± SD* *(range)*	*Tortuosity (0 to 4+)* *Mean ± SD* *(range)*
Normal	33	48 ± 20 (6 79)	322 ± 77 (110 427)	52 ± 10 (30 74)	2[illegible] ± 0[illegible] (1-4)
LVH	25	50 ± 20 (12 77)	619 ± 186 (288 1230)	60 ± 08 (46 76)	22 ± 08 (1-4)
Myocardiopathy	57	48 ± 18 (18 88)	691 ± 194 (380 1200)	62 ± 08 (48 86)	17 ± 0 (1-4)
RVH	30	50 ± 18 (10 83)	403 ± 121 (170 708)	54 ± 08 (34 66)	23 ± 07 (1 3)
Total	145	49 ± 18 (6 88)	538 ± 216 (110 1230)	58 ± 10 (30 86)	21 ± 07 (1-4)

D Diameter of theoretical single coronary artery
LVH Left ventricular hypertrophy
RVH Right ventricular hypertrophy
SD Standard deviation

Table II Linear correlation coefficients for selected variables in 145 hearts

	Log heart weight	*Log D_{Th}*	*Tortuosity*
Age	072	154	402
Log Heart weight		627	−237
Log D_{Th}			096

out multivariable regression analyses using Biomedical Computer Program BMDO2R [7]

Results

In the first review of the 738 coronary angiograms each usable case had been assigned to a category of severity of angiographically detectable coronary artery disease on a scale of 0 to 4+ In 145 hearts there was no vascular abnormality seen on the angiograms and at most only trivial atherosclerosis recorded from examination of the multiple transections of the coronary arteries made at 2 to 3 mm intervals These hearts with grade 0 arterial lesions were the only ones included in this study

The major characteristics of the disease groups and the total population are shown in Table I Correlation matrices were determined for the variables listed above and were analyzed Heart weight appeared to be the best expression of cardiac size Ventricular volumes left ventricular length and surface area and heart size relative to body size showed no better correlations and are derived from the heart size Tortuosity showed better correlations than tortuosity index Tortuosity, therefore was used for further analyses although the index provided a form of 'quantitative substantiation of the qualitative assessment of 0 to 4+ D_{Th} showed correlations as good as those obtained with the other measures of coronary artery caliber The logarithms of D_{Th} and logarithm of heart weight were selected to simplify graphing of the data The correlation coefficients for those relationships that were judged to be worthy of further investigation are shown in Table II

The relationship between D_{Th} and heart weight age and tortuosity An equation predicting the caliber of the theoretical single coronary artery from the heart weight the patient s age and epicardial coronary artery tortuosity was sought using multivariable regression analysis The program makes predictive formulas by choosing from up to 99 variables in the sequence of their F values for inclusion, and obtains a multivariable correlation coefficient as each significant variable is entered A separate formula for each disease category and the entire group was calculated which predicted log D_{Th} using the variables log heart weight age and tortuosity (Table III)

The formulas derived for the normal and LVH groups indicate that log D_{Th} is directly related to log heart size Conversion of the formulas shows that for the normal group (D_{Th}) [illegible] is proportional to heart weight and for LVH (D_{Th})[illegible] is proportional to heart weight In other words normal and normally proportioned but enlarged hearts

Table III Multivariable regression formulas for prediction of D_{Th}

Group	Number	*Formula using statistically significant (p < .05) variables*	*Multiple correlation coefficient (R)*	*Standard error of estimation*	*F to enter or remove*		
					Age	*Log heart weight*	*Tortuosity*
Normals	33	log D_{Th} = −0.18? + 0.360 log heart weight	0.59	0.07	3.11	16.76¶	2.99
LVH	25	log D_{Th} = −0.103 + 0.318 log heart weight	0.70	0.04	0.00	?2.12¶	0.17
Myocardiopathy	57	log D_{Th} = 0.109 + 0.?35 log heart weight + 0.031 tortuosity −0.001 age	0.61	0.05	4.48†	23.31¶	9.93‡
RVH	30	log D = −0.047 + 0.?18 log heart weight + 0.05? tortuosity	0.54	0.06	0.43	6.2?†	7.50†
All	145	log D_{Th} = 0.263 log heart weight + 0.025 tortuosity	0.67	0.0?	0.01	114.73¶	15.0?¶

* = not statistically significant ($p > .05$)
† = $p < .05$
‡ = $p < .01$
§ = $p < .005$
|| = $p < .001$
¶ = $p < .0005$

have coronary arteries which increase in size with cardiac growth so that their diameter cubed parallels heart size. This matching of coronary size and heart weight was evident up to heart weights of 1,230 Gm.

The analyses indicated that for myocardiopathy, RVH, and the entire group of 145 hearts a correction for tortuosity significantly improved the prediction of D_{Th}. The more tortuous, i.e., longer, the vessels the greater their diameter. Age is not per se a significant factor for predicting D_{Th} except in the myocardiopathy group where it was statistically significant but quantitatively unimportant.

The relationship between the tortuosity of the epicardial coronary arteries and age, D_{Th}, and heart weight. Predictive formulas of overall epicardial coronary artery tortuosity from the variables age, log D_{Th}, and log heart weight for each disease group separately and all 145 hearts were obtained. The results appear in Table IV and illustrate that age is the only significant factor in determining epicardial coronary artery tortuosity in the normal group and is the strongest, though not statistically significant, predictor in the LVH group. The myocardiopathy and RVH groups show a positive relationship with age and a negative relationship with heart weight. In addition, D_{Th} is entered into the formula for these two groups. The formula calculated for the entire group of 145 hearts shows that tortuosity is directly related to age and D_{Th} but inversely related to heart weight. In other words, as a person gets older or has enlargement of coronary caliber, tortuosity increases. If the heart size enlarges, tortuosity decreases, i.e., the vessels straighten, and if the heart shrinks, as in old age or debilitation, tortuosity increases.

Discussion

The study shows that coronary artery caliber varies relative to heart weight and in such a manner that D of the coronary arteries is directly proportional to heart weight. This result supports the concept that the blood flow volume required by the myocardium determines the size of the coronary arteries. The hearts included in the present study had angiographically normal coronary arteries and even those hearts with very large weight showed sufficient increase of arterial caliber to maintain normal flow rates for the mass of the heart. That D of the coronary arteries was found to be proportional to heart weight is consistent with the concept that the caliber of vessels is regulated in a manner to provide the maximum economy of energy expenditure.[1]

The theoretical single coronary artery supplying blood to the heart was used as a matter of convenience in making the calculations of the present study. It was determined from the rela-

Table I Characteristics of disease groups

Group	Number	*Age (years) Mean ± SD (range)*	*Heart weight (Gm) Mean ± SD (range)*	*D_{Th} (mm) Mean ± SD (range)*	*Tortuosity (0 to 4+) Mean ± SD (range)*
Normal	33	48 ± 20 (6 79)	322 ± 77 (110 427)	5 2 ± 1 0 (3 0 7 4)	2 2 ± 0 7 (1-4)
LVH	25	50 ± 20 (12 77)	619 ± 186 (288 1230)	6 0 ± 0 8 (4 6 7 6)	2 2 ± 0 8 (1-4)
Myocardiopathy	57	48 ± 18 (18 88)	691 ± 194 (380 1200)	6 2 ± 0 8 (4 8 8 6)	1 7 ± 0 7 (1-4)
RVH	30	50 ± 18 (10 83)	403 ± 121 (170 709)	5 4 ± 0 8 (3 4 6 6)	2 3 ± 0 7 (1 3)
Total	145	49 ± 18 (6 88)	538 ± 216 (110 1230)	5 8 ± 1 0 (3 0 8 6)	2 1 ± 0 7 (1 4)

D_{Th} Diameter of theoretical single coronary artery
LVH Left ventricular hypertrophy
RVH Right ventricular hypertrophy
SD Standard deviation

Table II Linear correlation coefficients for selected variables in 145 hearts

	Log heart weight	*Log D_{Th}*	*Tortuosity*
Age	072	154	402
Log Heart weight		627	− 237
Log D_{Th}			086

out multivariable regression analyses using Biomedical Computer Program BMDO2R [7]

Results

In the first review of the 738 coronary angiograms each usable case had been assigned to a category of severity of angiographically detectable coronary artery disease on a scale of 0 to 4+ In 145 hearts there was no vascular abnormality seen on the angiograms and at most only trivial atherosclerosis recorded from examination of the multiple transections of the coronary arteries made at 2 to 3 mm intervals These hearts with grade 0 arterial lesions were the only ones included in this study

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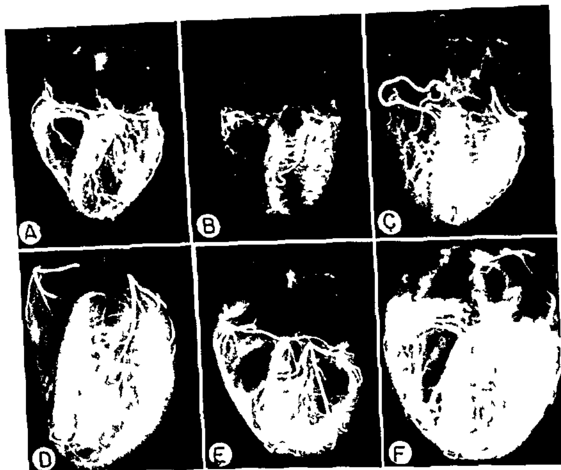


Fig. 1. Postmortem coronary arteriograms all shown at the same reduction of size. *A*, Normal 330 Gm. heart from a 29 year old female. There is 2+ or average tortuosity. *B*, Normal 300 Gm. heart from an 87 year-old male. Tortuosity is more marked (3+) than in *A*. *C*, Heart with myocardiopathy due to mitral regurgitation, weighing 600 Gm., from a 8-year-old female. Tortuosity is extreme (4+) with several arteries forming complete loops. *D*, Myocardiopathy caused by rapid progression of aortic regurgitation in a 1065 Gm. heart from an 18-year old male. These coronary arteries were the straightest, or least tortuous (1+) encountered in this study. *E*, Idiopathic myocardiopathy in a 550 Gm. heart from a 42 year old male. There is less than average tortuosity. *F*, Idiopathic myocardiopathy in an 885 Gm. heart from a 35 year old male. In comparison to *D* there is much greater tortuosity despite the marked ventricular dilatation. Presumably tortuosity increased concurrently with the increase of arterial caliber induced by myocardial hypertrophy.

longitudinal dimension of the artery. As explained above, increase in caliber of the coronary arteries is principally related to an increase in heart weight. Cardiac enlargement then produces tortuosity increase by the associated coronary arterial dilatation but also decreases tortuosity by expanding the epicardial surface and straightening the arteries. Both processes occur at the same time so that the net effect on tortuosity is small, particularly when compared to the age-related change. Thus, the general interpretation of coronary arterial tortuosity appears to be that the epicardial coronary arteries are straightened by dilatation of the heart, and made more tortuous mostly by shrinkage of the heart and also to a lesser degree by lengthening accompanying the increased arterial diameter which is a response to increased blood flow (Fig. 1). The functional significance of tortuosity in terms of resistance to blood flow or blood turbulence is uncertain.

It appears clear from this study that normal coronary arteries increase in caliber proportional to the demands of an enlarging heart and this was evident even when hearts exceeded 1,000 Gm. Thus, there is no evidence that even these enormously hypertrophied hearts outstrip their epicardial blood supply. It is evident, however,

Table IV Multivariable regression formulas for prediction of tortuosity

Group	Number	Formula using statistically significant ($p < 05$) or strongest variables	Multiple correlation coefficient (R)	Standard error of estimation	F to enter or remove		
					Age	Log heart weight	Log D_m
Normal	33	Tort = 1 078 + 0 016 age	0 48	0 59	9 24‡	0 05	0 6
LVH	25	Tort = 1 205 + 0 014 age	0 34	0 79	2 95	0 2	0 00
Myocardiopathy	57	Tort = 1 960 + 0 018 age −1 816 log heart weight + 5 159 log D_r	0 56	0 59	15 26¶	6 43†	9 93§
RVH	30	Tort = 5 181 + 0 012 Age −2 001 log heart weight + 3 195 log D_r	0 61	0 54	4 34†	7 10†	4 38
Total	145	Tort = 4 320 + 0 015 age −1 782 log heart weight + 3 178 log D_m	0 54	0 63	29 08¶	25 85¶	11 85

= not statistically significant ($p > 05$)
† = $p < 05$
‡ = $p < 01$
§ = $p < 005$
= $p < 001$
¶ = $p < 000$

tionship that the cube of the diameter of a parent vessel equals the sum of the cubes of the diameters of its branches This formula, which had been predicted on the basis of theoretical considerations of the blood flow being governed by the principle of minimum work has been shown by direct measurement to accurately describe the branches of the normal coronary arterial tree

The multivariable regression analysis shows that in addition to heart weight tortuosity of the coronary arteries contributes to predicting the caliber of the coronary arteries (Table III) and is of slightly greater significance than heart weight for the RVH group We are unable to account for the latter observation by any feature noted in the RVH cases In general however the increase in coronary artery length relative to distance traveled that produces tortuosity increases resistance to flow The energy lost by this greater length could be compensated for by dilatation of the vessel Alternatively as suggested below the same factors that produce tortuosity produce dilatation

When the tortuosity was predicted by multivariable regression analysis for the various groups it was found that age heart size and coronary caliber all made significant contributions (Table IV) It appears that age is the most important determinant in predicting increased epicardial coronary artery tortuosity Increased heart weight leads to a decrease in arterial tortuosity but increase in coronary artery diameter is associated with increased tortuosity Reexamination of the data from the 145 cases suggested that the inverse relationship between tortuosity and heart weight was caused by the low tortuosity in the dilated hypertrophied hearts of the myocardiopathy group Presumably dilatation of the ventricle which is of course greater in these hearts than hearts of comparable size in the other groups leads to a straightening of the epicardial coronary arteries The reason for increased tortuosity with age is unexplained by the results of this study It is probable however, that in patients surviving into old age there may be a decrease in heart size due to a reduction in activity [11] Such a shrinkage of ventricular mass could produce an increased tortuosity of the epicardial arteries Thus age, per se may not account for the arterial tortuosity of the elderly since presumably tortuosity would increase if heart size decreased in any patient as for example with cachexia The increased arterial tortuosity associated with larger arterial caliber may mean that the same process which produces arterial dilatation leads to a comparable increase in the

A comparison of the response to arm and leg work in patients with ischemic heart disease

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Graded exercise testing is now a well established tool for clinical evaluation of patients with ischemic heart disease Standard methods require leg work but alternate methods involving arm work should be available for patients who cannot perform leg work patients who complain of angina preferentially with arm work and for patients with a history suggesting angina but negative standard test Previous clinical experi ence is limited but there is evidence to suggest that arm crank ergometry may provide a useful alternative to standard bicycle or treadmill exer cise The purpose of this study was to evaluate an exercise test based on arm work in a group of patients with documented ischemic heart disease and to compare the response to leg and arm work in a group of patients with a history of angina pectoris predominantly precipitated by arm work

Methods and material

The study group included 33 patients all male The age range was 42 to 67 years with a mean age of 52 years All patients had objective evidence of arteriosclerotic heart disease Fourteen patients had coronary angiography and demonstrated at least one significant coronary arterial obstruction (at least 75 per cent reduction of the cross sectional area of a major coronary artery) and 19 patients had prior myocardial infarction docu mented by typical history evolutionary ECG abnormalities and significant serum enzyme abnormalities (SGOT CPK LDH) Patients with recent myocardial infarction (less than 3 months) unstable angina pectoris or ventricular arrhythmias at rest other than infrequent PVC s were excluded as were patients with peripheral vascular disease or resting blood pressure above 150/90 mm Hg

Arm and leg exercise was performed in alter nating order on the same day with an interval of 1 to 4 hours between tests The target level was a rate of work producing 90 per cent of the esti mated age specific maximal heart rate[5] but exer cise was discontinued if the patient complained of chest pain consistent with angina and/or devel oped significant ST abnormalities i e horizontal ST depression or elevation $\geq$ 1 0 mm or ventric ular irritability defined as premature ventricular beats at a rate greater than 1/10 normal beats multifocal beats or couplets Other indications for discontinuing exercise conformed to the stan dards presented by Rochmis and Blackburn[6]

The arm crank device used was a modified table mounted mechanical bicycle ergometer (Monark) with removable handles fitted over the pedals (Fig 1) The patients were seated so that the midpoint of the sprocket was shoulder high for each patient The cranking speed was 50 revolutions per minute All patients started with 3 minutes at zero work load i e a load equal to internal resistance of the ergometer and the load was then increased by 150 *kilopond meters/minute* (kpm /min) every 3 *minutes* The electro cardiogram was continuously monitored and recorded using a modification of Frank s ortho

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that atherosclerotic narrowing of a coronary artery is a complete reversal of this normal situation in that coronary artery caliber decreases secondary to the intraluminal disease as the heart itself is frequently enlarging

Summary

Whether or not the size of the epicardial coronary arteries can increase to keep pace with cardiac mass in abnormally enlarged hearts, and what the mathematical relationship is between the enlarging heart and its vascular tree has been uncertain Relationships were sought between patient's age heart weight coronary artery caliber and tortuosity of epicardial coronary arteries in 145 cases with normal coronary arteries as judged by postmortem arteriography The hearts were normal (33 cases) or had left ventricular hypertrophy (25 cases) right ventricular hypertrophy (30 cases), or myocardiopathy (57 cases) as a predominant pathological finding Multivariable regression analysis for prediction of coronary artery caliber showed a direct linear relationship between heart weight and arterial diameter raised to the third power for normal hearts and those with left ventricular hypertrophy Although coronary caliber was principally related to heart size tortuosity which may be considered as length relative to distance traveled also contributed to its prediction in the whole group Tortuosity itself was predicted by an equation combining age positively and heart weight negatively to about equal importance and, to a lesser extent arterial caliber positively Tortuosity increases with age and with cardiac shrinkage, it increases in parallel with increase in coronary arterial caliber but decreases with cardiac enlargement The results show that normal coronary arteries enlarge their caliber by at least the cube of the diameter proportionate to increase in heart size It appears that this increase in caliber should be sufficient to maintain adequate blood flow to the myocardium and even very large hearts would not outstrip their blood supply

Mr Richard R Smith assisted in the collection of data for this study

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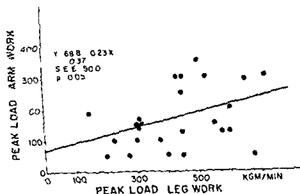


Fig 2 Correlation between peak work load during arm and leg exercise individual data

test was discontinued because of objective and/or subjective manifestations of myocardial ischemia in about two thirds of the patients (23/33 during leg work and 24/33 during arm work) of fatigue or shortness of breath in the remaining one third

Twenty six of 33 patients or 79 per cent had identical endpoints with both tests Three patients had an ischemic response (abnormal ECG during exercise and/or chest pain) to leg work only and four had ischemic response to arm work only The rate-pressure products (i e heart rate × systolic blood pressure × 10 ²) were not significantly different during arm and leg work in this subgroup Mean values were 222 during leg work and 209 units during arm work Individual differences were small and did not correlate with the presence or absence of signs and/or symptoms of myocardial ischemia

The peak work load during arm work 181 kpm/min was only 41 per cent of the peak load 439 kpm/min during leg work This difference was highly significant ($p < 0.001$) Individual work load data appear in Fig 2 The correlation between peak work loads during arm work and leg work was significant ($p < 0.05$) but relatively weak with an r value of 0 37 Peak heart rate was slightly higher during leg work 129 beats/min compared to 122 beats/min ($p < 0.05$) The rate-pressure product was also slightly higher during leg work 254 compared to 234 units but this difference was not significant The correlations between peak heart rates during arm and leg work was highly significant ($p < 0.01$ $r = 0.64$) The same was true for the peak rate-pressure products ($p < 0.01$ $r = 0.59$) Figs 3 to 5 show heart rate systolic blood pressure and rate pressure product during arm and leg exercise Mean

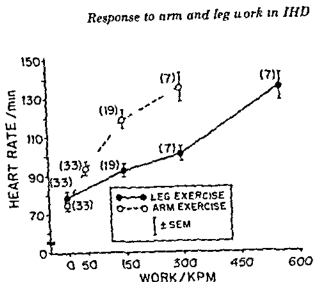


Fig 3 Mean heart rate at rest and during arm and leg exercise Numbers within brackets indicate number of patients Only patients with measurements during both arm and leg exercise at a given load have been included

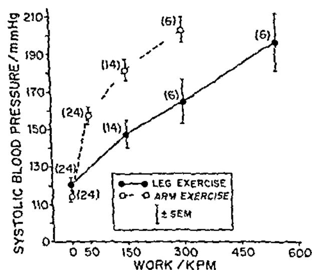


Fig 4 Mean systolic blood pressure at rest and during arm and leg exercise Symbols as in Fig 3

values at loads of 150 and 300 kpm/min include only patients who completed both loads during both forms of exercise The differences (paired t test) were highly significant ($p < 0.001$) with higher values during arm work Heart rate and systolic blood pressure increased with increasing work loads approximately twice as rapidly during arm work as during leg work Mean values at 600 kpm/min during leg work were not significantly different from mean values at 300 kpm/min during arm work

The apparent curvilinearity of the heart rate and blood pressure responses to arm work was

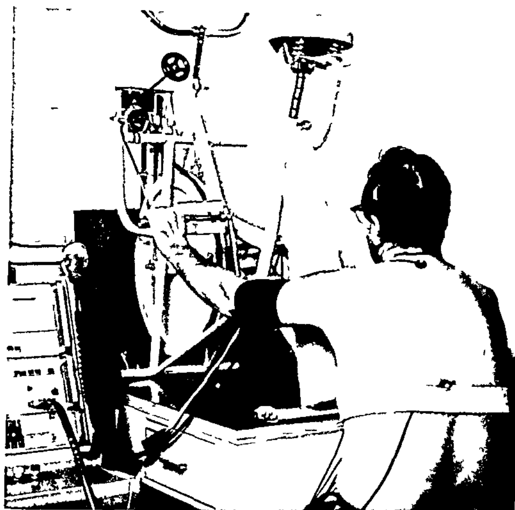


Fig 1 Standard mechanical bicycle ergometer modified for arm work Removable handles have been fitted over the pedals Clamps secure the ergometer to a sturdy table

Table I End points during arm and leg exercise in 33 patients with documented ischemic heart disease

End point	Leg exercise		Arm exercise	
	No of patients	*Per cent*	*No of patients*	*Per cent*
Abnormal ECG and chest pain	11	33	14	43
Abnormal ECG no chest pain	5	15	5	15
Chest pain normal ECG	7	21	5	15
Fatigue or short ness of breath	10	31	9	27
Totals	33	100	33	100

gonal lead system[7] Indirect arterial blood pressure (BP) was measured in the left arm with an Arteriosonde (Roche) machine at 2 minutes 30 seconds during each work period This measurement was accomplished by briefly permitting the left arm to hang while the patient continued to crank with the right arm A rest period of one minute s duration was interspersed between each work load Blood pressure measurements were obtained only immediately post exercise in the initial eight patients studied The pressures conformed to the pattern seen during exercise for the remaining 25 patients but have not been included in the analysis Interpretable electrocardiographic tracings were obtained during exercise but motion artifacts were often present The work free interval was inserted to produce an ECG of optimal quality

The leg work test also employed a mechanical bicycle ergometer (Monark) and 3 minute exercise stages utilizing 150 kpm /min increments Leg exercise was continuous The patient was instructed to take his left arm off the handle bar during the blood pressure measurement but continued pedaling at a constant rate

Results

A comparison of *endpoints* during arm and leg exercise is presented in Table I In both cases the

Table II Response to arm and leg exercise in patients with and without a history of arm work sensitivity Mean values ± S E E at peak loads

	Workload (kpm./min)		*Heart rate (beats/min)*		*Rate pressure product*	
	Arm work	*Leg work*	*Arm work*	*Leg work*	*Arm work*	*Leg work*
Patients with arm work sensitivity (N = 7)	200 ± 35	502 ± 50	139 ± 10	145 ± 7	235 ± 22	262 ± 22
Patients without arm work sensitivity (N = 18)	153 ± 23	409 ± 37	122 ± 6	129 ± 4	234 ± 16	250 ± 13

methods Clausen and Trap Jensen recently reported a consistently higher threshold of myocardial ischemia during arm work in a series of 12 patients studied before and after physical training ST abnormalities were present in a majority of their patients but only onset of angina was used to establish end points Peak heart rates systolic blood pressures and rate-pressure products were uniformly higher during arm work

Physiological correlates of sensitivity to arm work by history Some patients with angina may have chest pain during arm work but state that they are asymptomatic during leg work There are no previous studies specifically dealing with this category of patients A subgroup of seven patients had a history of angina pectoris preferentially being produced by arm work and their test responses were compared to those of the remaining 26 patients in the present series The comparison did not reveal any major physiologic differences Peak work loads during leg work were not statistically different but somewhat higher in the group with arm work sensitivity Levels of energy expenditure during leg work in the two groups roughly corresponded to walking speeds of 4 5 and 3 5 m p h The average patient in the arm work sensitive group would not be expected to have angina unless he walked at fairly brisk pace Thus it seems likely that a history of angina predominantly produced by arm work simply should be interpreted as indicating that the patient in his daily life reaches higher levels of myocardial oxygen demand and exceeds the threshold of myocardial ischemia more frequently during activities involving arm work than during walking

Mechanical efficiency during arm work and leg work Mechanical efficiency or the ratio between the output of external work and caloric expenditure is lower during arm work Oxygen uptake was not measured in the present study but the significantly lower peak work loads during arm work in patients who were not limited by myocardial ischemia are consistent with decreased mechanical efficiency This is attributable to the isometric component of arm work which increases oxygen uptake but does not affect the output of external work The correlation between peak loads during arm and leg work was tenuous (Fig 2) Thus while arm work is a valid clinical test method with respect to myocardial ischemia measurements of physical work capacity defined as aerobic capacity cannot be based on arm work

Hemodynamic considerations Heart rates systolic blood pressure and rate pressure products at angina are similar during arm and leg work but studies in normal subjects have demonstrated significant hemodynamic differences some of which may have important effects on the relation between myocardial oxygen demand and supply Stroke volume is lower during arm work at any given level of afterload at equivalent heart rates This suggests that the end diastolic volume may be smaller during arm work which would decrease wall tension and myocardial oxygen demand at any given intraventricular pressure Furthermore pulse pressures are consistently lower during arm work Higher diastolic arterial pressures at comparable levels of heart rate and systolic pressure during arm work should further improve the relation between myocardial oxygen supply and demand by increasing diastolic perfusion pressure and coronary flow However the results of this study and previous data on arm work in patients with ischemic heart disease provide no evidence to support these considerations with the exception of the results presented by Clausen and Trap Jensen Studies of coronary blood flow during dynamic and isometric exercise[9-11] in normal subjects and of heart rate and arterial pressure in patients with angina pectoris during daily life

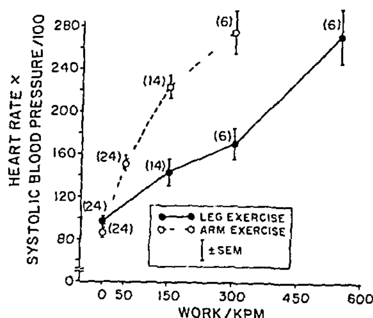


Fig 5 Mean rate pressure product at rest and during arm and leg exercise Symbols as in *Fig 3*

due to more rapid increase in patients with low work tolerance Individual responses were generally linear

A subset of seven patients gave a history of angina which was often precipitated by arm work but rarely by walking Four of these patients had identical endpoints on both arm and leg tests Of the three patients with dissimilar endpoints two had positive arm and negative leg tests and one patient had a positive leg and negative arm test Heart rate and blood pressure responses to increasing loads during arm and leg work followed a similar pattern in patients with and without a history of sensitivity to arm work, i e higher values during arm work at any given submaximal load but no significant differences at peak loads Peak work loads heart rates and systolic blood pressures tended to be higher in the arm work sensitive group than in the remainder of the series both during arm and leg work but the differences were not statistically significant (Table II)

Discussion

Most information on the response to exercise in patients with heart disease is based on standard forms of treadmill or bicycle exercise Only recently have detailed clinical studies or other activities become available e g isometric exercise and arm exercise More information is needed to provide a better understanding of the relation between findings during formal exercise tests and the cardiovascular effects of daily life activities There is also a need to establish alternate test procedures for patients who for one reason or another cannot perform the type of exercise required by standard test procedures

The present study utilized a standard and a modified bicycle ergometer for comparison of the response to leg and arm work in a series of patients with documented ischemic heart disease The exercise mode included the basic feature of most forms of arm work performed during daily life activities i e , a combination of isometric and dynamic effort The isometric component may be more or less evident during the wide range of occupational and recreational activities that involve arm work, but there is generally a sustained isometric effort gripping handling and supporting various implements

Clinical value of an exercise test based on arm work Arm work produced ischemic responses with the same frequency as leg work but at a reduced work load i e at about 40 per cent of the peak load reached during leg work The threshold levels of myocardial ischemia, measured as the rate-pressure product at angina and/or the appearance of significant ST abnormality and endpoints were similar for both types of work These findings support the use of arm exercise as an alternate clinical exercise test method fo precipitation and documentation of myocardial ischemia Wahren and Bygdeman studied 10 patients performing arm and leg work of the same type as used in our study Angina was produced in all patients by both types of exercise and at similar levels of myocardial oxygen demand as judged by rate pressure products and triple products (heart rate × systolic mean blood pressure × ejection period) Total body oxygen uptake at angina was slightly but significantly lower during arm work Shaw and colleagues' compared treadmill exercise and arm crank ergometry using a modified bicycle ergometer with two handles fitted on a single pedal Peak heart rate in 21 patients including 17 with documented ASHD was slightly lower during arm work but peak systolic pressure and the rate-pressure products were not significantly different Ten patients had ischemic and 10 patients had normal ECG responses to both methods Discordant results were seen only in a single patient Shaw and associates also demonstrated similar peak heart rates and systolic blood pressures in separate groups of ten patients who were tested by one or the other of the two

Case reports

Partial anomalous pulmonary venous connection (intact atrial septum) associated with mitral regurgitation

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The incidence of pulmonary venous drainage into the right heart in adults during routine autopsy examination has been reported to be 0 7 per cent Partial anomalous pulmonary venous connection (PAPVC) almost invariably coexists with an atrial septal defect and only rarely occurs as an isolated anomaly The association of PAPVC with various other congenital cardiovascular lesions has also been reported The association of PAPVC with mitral stenosis has received the greatest attention Thirty patients have been reported in the English literature who had both PAPVC and mitral stenosis which was of rheumatic origin in all but one case Twenty five had pure stenosis and five had combined stenosis and regurgitation The present report describes two patients who had PAPVC with intact atrial septum associated with isolated severe nonrheumatic mitral regurgitation To our knowledge this association has been reported on only one previous occasion

Report of cases

Case 1 This white woman was first seen at the Mayo Clinic in August 19 1 at the age of ?3 years A heart murmur had been discovered at her birth and at the age of 11 years she was thought to have had a mild attack of rheumatic fever At 19 she experienced pain swelling and redness of the ankles and knees associated with fever malaise and conjunctival hemorrhage The cardiac silhouette was enlarged and a Grade 4/6 apical systolic murmur was present She was hospitalized for 6 weeks and was treated for subacute bacterial endocarditis with penicillin intravenously Since then she had remained essentially asymptomatic and was subsequently referred to this clinic for evaluation of "aortic and mitral valve disease

Physical examination revealed a height of 6 inches and weight of 1 6 pounds pulse at ?0 per minute and blood pressure of 1?0 ?o mm Hg Jugular venous pressure was normal Carotid upstroke was brisk and all peripheral pulses were intact The apex impulse was displaced ? 5 cm lateral to the midclavicular line A coarse systolic apical thrill an apical thrust and a left parasternal lift were palpable The first heart sound was soft The second heart sound was widely split A Grade 5/6 holosystolic murmur was heard at the apex and this murmur radiated to the left axilla and back A separate Grade 1/6 ejection systolic murmur and a Grade 1/6 early diastolic murmur were heard along the left sternal edge The clinical diagnosis was severe mitral regurgitation due to ruptured chordae tendineae secondary to previous subacute bacterial endocarditis In addition the patient was thought to have trivial aortic regurgitation The electrocardiogram (ECG) and the vectorcardiogram are shown in Fig 1 Roentgenogram of the chest (Fig 2 A) and cardiac fluoroscopy revealed left ventricular and left atrial enlargement increased pulmonary vascular markings and no intracardiac calcification

The echocardiographic findings revealed a slightly increased right ventricular dimension associated with normal ventricular septal motion These findings have previously been reported

Right and left heart catheterization and selective left ventricular and right pulmonary artery angiography were performed The hemodynamic summary is shown in Table I The left ventricular angiogram revealed severe mitral regurgitation with dense filling of an enlarged left atrium A pulmonary artery angiogram revealed that both pulmonary arteries were normal The entire venous return from the right lung drained anomalously into the superior vena cava Before the angiocardiogram a left to right shunt at the superior vena cava level had been demonstrated (see Fig ?)

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activities[12,13] have failed to demonstrate any significant beneficial effects of relative increase of diastolic arterial pressures It is tempting to speculate that isometric effort may be associated with a reflex increase in coronary vascular resistance offsetting the increase in perfusion pressure, and there is, in fact, preliminary experimental data to support this hypothesis[14]

Summary

An exercise test based on arm work was evaluated in a series of 33 male patients, mean age 52 years with ischemic heart disease The responses to arm exercise on a modified table mounted bicycle ergometer and to standard bicycle exercise were compared

Twenty six of 33 patients (79 per cent) had identical end points with both tests Three patients had an ischemic response, i e , significant ST abnormality and/or angina pectoris during leg work only, and four patients during arm work only Peak workload during arm exercise was only 41 per cent of the peakload during leg exercise Mean values were 181 and 439 kpm/min ($p < 0.001$) Comparison of individual data on peak load demonstrated only a weak correlation between arm and leg work capacity ($r = 0.37$, $p < 0.05$) Peak heart rate was slightly higher during leg work, 129 compared to 122 beats/min ($p < 0.05$) but the mean heart rate systolic blood pressure products were not significantly different

A subgroup of seven patients had a history of angina pectoris preferentially precipitated by arm work but their physiological responses did not differ significantly from those of patients without a history of arm work sensitivity

The data indicate that arm work is a satisfactory alternate diagnostic test method with respect to myocardial ischemia, but measurements of physical work capacity defined as aerobic capacity cannot be based on arm work

We wish to extend our appreciation for the important technical aid given to this study by Ms Janet Park

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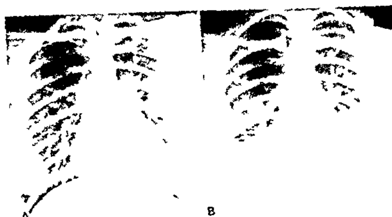


Fig 2 Case 1 A Chest roentgenogram (preoperative) Moderate generalized cardiomegaly with left atrial enlargement prominent left ventricle and increased pulmonary vascular markings B Chest roentgenogram taken 1 year postoperatively There has been considerable regression in heart size and pulmonary vascularity

with a presystolic sound The second heart sound was narrowly split varying little with inspiration and had an accentuated pulmonic component The rest of the physical examination was unremarkable

The clinical impression was severe mitral regurgitation secondary to ruptured chordae tendineae most probably resulting from recent bacterial endocarditis

Roentgenogram of the chest revealed cardiac enlargement and increased pulmonary vascularity suggestive of left to right shunt (Fig 3 A) Cardiac fluoroscopy confirmed biventricular enlargement and showed increased pulmonary vascularity No valvular calcification was noted Fig 4 depicts the ECG and vectorcardiogram of this patient An echocardiogram revealed increased right ventricular dimension associated with normal ventricular septal motion Right and left heart catheterization was performed The hemodynamic summary is presented in Table II

A selective left ventricular angiocardiogram revealed a moderately enlarged hypertrophied chamber with reasonably good contractility Severe mitral regurgitation resulting in dense opacification of a small left atrium was demonstrated The interatrial septum was intact

Because the dye curve with injection into the left pulmonary artery was normal whereas that from the right pulmonary artery had shown left to right shunt (Fig 5) a selective right pulmonary artery angiogram was performed The venous phase of this angiogram revealed the anomalous drainage of the right superior pulmonary vein into the superior vena cava The veins from the right middle and lower lobes were connected normally to the left atrium (Fig 6)

At operation a persistent left superior vena cava was also incidentally noted The right atrium was moderately enlarged whereas the left atrium was small The anomalous vein joined the superior vena cava 2 cm above the junction with the right atrium The atrial septum was intact An atrial septal defect was created and by means of a pericardial patch tunnel the anomalous drainage was diverted into the left atrium Both mitral leaflets were soft pliable and intact as were the chordae tendineae and no stigma of bacterial endocarditis was noted Initially an annuloplasty was performed but was found to be unsuccessful because of a high left atrial pressure and persistence of a systolic thrill over the left atrium The mitral valve was therefore excised and replaced by a Starr Edwards cloth covered ball valve prosthesis

After a somewhat difficult postoperative course with respiratory problems the patient was dismissed on long term anticoagulant therapy

He returned for recheck 3 months later He was much improved and would experience only minimal breathlessness on heavy exertion The mitral prosthesis sound were normal A Grade 2/6 apical systolic murmur was heard The cardiac

Table I Hemodynamic summary of case 1

Site	Pressure (mm Hg)	% Saturation
Brachial artery	145/85 (m = 105)	96
Aorta	145/84	—
Left ventricle	145/6 10	—
Left pulmonary artery wedge	a = 17 v = 15 (m = 10)	9
Right pulmonary artery wedge	a = 15 v = 16 (m = 14)	98
Main pulmonary artery	3 /16 (m = 22)	86
Right ventricle	38/0-11	87
Right atrium (mid)	a = 14 v = 11 (m = 12)	81
Low superior vena cava	—	91
High superior vena cava	—	7

Pulmonary index (Fick) = 6 5 L per minute per square meter
Systemic index = 3 / L per minute per square meter
Qp/Qs = 1 7
Per cent left to right shunt (Fick) = 45
Pulmonary resistance = 3 4 UM
Pulmonary arteriolar resistance = 1 5 UM
Systemic resistance = 28 UM

a = atrial v = ventricular m = mean

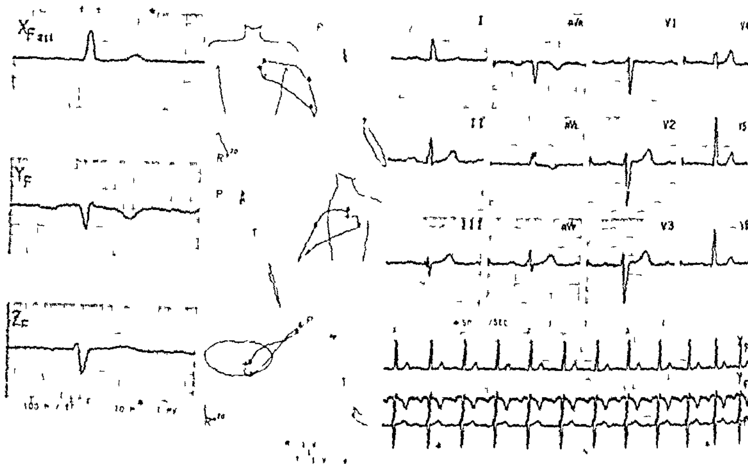


Fig 1 Case 1 ECG and vectorcardiogram showing sinus rhythm rate of 83 per minute first degree A V conduction delay (P R interval 0.22 sec) left atrial conduction delay and left ventricular enlargement

At operation the anomalous venous return from the entire right lung was found to enter the superior vena cava 2 cm above the atriocaval junction The interatrial septum was intact A strong systolic thrill was palpated on the posterior left atrial wall Examination of the mitral valve revealed a complete cleft of the anterior leaflet identical to that seen in patients with atrioventricular canal defects Apart from this the mitral valve apparatus appeared normal No stigma of bacterial endocarditis was seen The interventricular septum was intact With cardiopulmonary bypass the atrial septum was incised and through this opening the cleft in the anterior mitral leaflet was completely repaired Then a tunnel was created with a pericardial patch and through this the venous return from the right lung was diverted into the left atrium The superior vena cava was also enlarged by means of a pericardial patch After the bypass was discontinued only a small residual systolic thrill was present on the posterior left atrial wall indicating a satisfactory repair of the cleft and hence of mitral regurgitation

The postoperative course was uneventful and the patient who was in sinus rhythm was dismissed without any cardiac medication

She returned 1 year later (October 1972) for recheck In the interim she had experienced an episode of pleuritic chest pain cough and slight hemoptysis 6 months after surgery without recurrence She had also suffered from three separate brief paroxysms of rapid heart action but she was otherwise asymptomatic with normal effort tolerance Physical examination revealed normal jugular venous pressure and carotid upstroke The precordial overactivity was no longer present A Grade 1/6 holosystolic apical murmur was heard The second heart sound was still widely split The cardiac silhouette had decreased (Fig 2 B) and the ECG evidence of left ventricular hypertrophy had also diminished

Case 2 This 51 year old man was first seen at the Mayo Clinic in February 1972 He had been in good health until November 1971 when a respiratory tract infection developed Roentgenogram of the chest was reported to be normal but over the next 10 days he became aware of exertional breathlessness and repeat chest x ray at that time showed cardiac enlargement He also complained of pleuritic type chest discomfort The patient was hospitalized for 3 weeks during which time he experienced a temperature elevation each afternoon to about 102° F A heart murmur was discovered during this examination and in spite of many negative blood cultures he was treated presumptively as having bacterial endocarditis he received penicillin intravenously for 3 weeks At the time the patient was discharged from the hospital his fever had subsided and the cardiac silhouette had decreased in size He was given a regimen of digoxin and furosemide (Lasix) and did not return to work Over the next 2 months exercise tolerance deteriorated further and heart size increased exertional breathlessness was his only symptom The patient was referred to this clinic for further cardiac evaluation

Physical examination revealed a height of 61 8 inches and weight 159 pounds pulse at 104 per minute and a blood pressure of 110 80 mm Hg The precordium was overactive A left parasternal lift an apical thrust and an apical systolic thrill were palpated A Grade 4/6 harsh pansystolic murmur was heard at the apex with radiation to the axilla and to the left sternal border A soft third heart sound followed by a Grade 1/6 diastolic murmur at the apex were also noted along

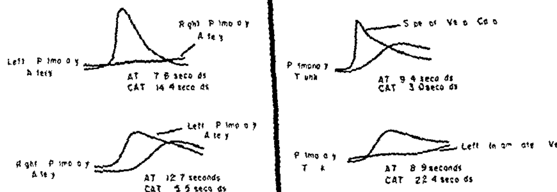


Fig 5 Case 2 Central sampling indicator dilution dye curves With dye injection into left pulmonary artery no early dye appears in right pulmonary artery when samples are taken simultaneously from this site and femoral artery (upper left) However dye curves (lower left) show early dye in left pulmonary artery after injection into right pulmonary artery This establishes presence of left to right shunt which is localized to superior vena cava level (upper right) where dye again appears early at central sampling site when compared with more proximal innominate vein (lower right) AT = appearance time CAT = corrected appearance time All systemic sampling sites from femoral artery Injection site shown on left of figure central sampling sites on right Indicator 5 mg of indocyanine green



Fig 6 Case 2 Biplane pulmonary angiogram *A* Early phase of a pulmonary arterial angiogram showing large pulmonary arteries with a normal pattern *B* and *C* Anteroposterior and lateral views respectively of levophase of pulmonary angiogram demonstrating drainage of pulmonary veins from upper (and middle) lobe of right lung into superior vena cava (arrows) with opacification of right atrium

The diagnosis of associated PAPVC in both cases was established by right heart catheterization indocyanine green indicator dilution curves and pulmonary angiography Both patients had some features in common clinically severe mitral regurgitation an episode resembling subacute bacterial endocarditis and a clinical diagnosis of ruptured chordae tendineae The cause of the mitral regurgitation however was quite different in each patient The mitral regurgitation in the first patient was due to a congenitally cleft anterior mitral leaflet Although this was identical to that seen in patients with an atrioventricular canal defect the vectorcardiogram (Fig 3) did not show a superiorly oriented counterclockwise frontal plane loop so typical of this abnormality Similarly the appearances of the left ventricular outflow tract on cineangiography were not consistent with an A V canal defect Therefore in this patient both the lesions were of developmental origin and this represents the first reported instance of such an association The cause of the mitral regurgitation in the second patient remains undetermined This patient s clinical course hemodynamic findings and normal sized left atrium are features that point to


A B

Fig 3 Case 2 *A* Chest roentgenogram (*preoperative*) Marked cardiac enlargement with prominence of main pulmonary artery segment and pulmonary vasculature *B* Chest roentgenogram (postoperative) There has been a decrease in over all heart size pulmonary artery size and pulmonary vascularity Mitral prosthesis is normally situated

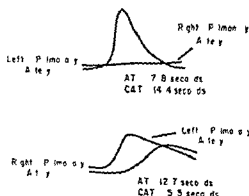
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Fig 4 Case 2 ECG and vectorcardiogram showing sinus rhythm with a rate of 95 per minute vertical QRS axis prominent anterior initial QRS forces but no definite evidence of left or right ventricular hypertrophy

size had decreased slightly since surgery (Fig 3 *B*) however no significant change was noted in the ECG One year after surgery there had been no appreciable further change in the clinical ECG or radiologic findings and a NYHA functional Class II status was maintained Digitalis and diuretics were continued The patient declined further catheter study

Comment

The presence of isolated PAPVC can be suspected if the physical findings resemble those found in patients with atrial septal defect However, if valvular heart disease coexists, then the findings are usually typical of the valvular lesion This was so in both of our patients as they presented with physical signs of mitral regurgitation There were no clues as to the presence of associated left to right shunt in the first patient but on the basis of the chest roentgenogram this possibility was entertained in the second patient



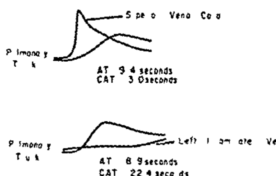


Fig 5 Case 2 Central sampling indicator dilution dye curves With dye injection into left pulmonary artery no early dye appears in right pulmonary artery when samples are taken simultaneously from this site and femoral artery (upper left) However dye curves (lower left) show early dye in left pulmonary artery after injection into right pulmonary artery This establishes presence of left to right shunt which is localized to superior vena cava level (upper right) where dye again appears early at central sampling site when compared with more proximal innominate vein (lower right) *AT* = appearance time *CAT* = corrected appearance time All systemic sampling sites from femoral artery Injection site shown on left of figure central sampling sites on right Indicator 5 mg of indocyanine green



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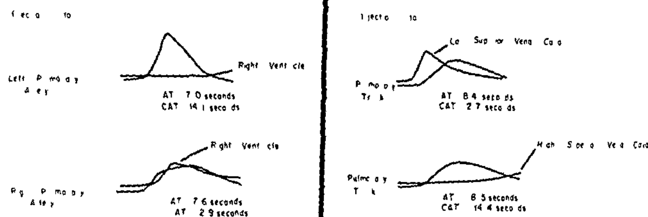


Fig 7 Case 1 Central sampling indicator dilution dye curve With right ventricle as central sampling site no early appearing dye is seen here compared with brachial artery after left pulmonary artery dye injection (upper left) Dye curves (lower left) show *that a large amount of early dye is present in right ventricle after dye injection* into right pulmonary artery Similar pattern is observed (upper right) with sampling in low superior vena cava and site of shunt is established at this level by absence of early dye in high superior vena cava (lower right) *AT* = appearance time *CAT* = corrected appearance time All systemic sampling sites from brachial artery Injection site shown on left of figure Central sampling sites on right Indicator 5 mg of indocyanine green

Table II Hemodynamic summary of case 2

Site	*Pressure (mm Hg)**	*% Saturation*
Femoral artery	130/89 (m = 102)	96
Aorta	117/86	–
Left ventricle	*116/13 26*	–
Pulmonary wedge (RI L)	a = 25 v = 36 (m = 24)	–
Main pulmonary artery	86/39 (m = 48)	79
Right ventricle	85/7 25	–
Right atrium (mid)	a = 22 v = 19 (m = 17)	80
Superior vena cava	*22/2*	87
Subclavian vein	–	67
Inferior vena cava	–	68

Pulmonary index (Fick) = 3 4 L per minute per square meter
Systemic index = 2 1 L per minute per square meter
Qp/Qs = 1 6
Per cent left to right shunt (Fick) = 41
Pulmonary resistance = 15 UM
Pulmonary *arteriolar resistance* = 6 UM
Systemic resistance = 49 UM

a = atrial v = ventricular m = mean

severe mitral regurgitation of recent onset Although ruptured chordae tendineae might be expected in this situation at surgery all chordae tendineae were intact and the mitral leaflets were soft and pliable There was *no stigma of* rheumatic fever or bacterial endocarditis This was *of particular* interest as successful manage ment of this entirely unexplained mitral regurgitation could be achieved only by mitral valve replacement Postoperatively this patient remains symptomatic and it cannot be excluded that he may have some form of myocardial disease

Comparison of wedge pressures from normally and anomalously draining lung segments has produced interesting observations *There have been a number of reports of cases of PAPVC to the superior vena cava or right atrium associated* with mitral stenosis and intact atrial septum in which disparate pulmonary arterial wedge pressure recordings from different parts of the same lung have been outlined This difference can be easily *understood since the wedge pressure of the* anomalously draining segment will reflect the lower right heart pressure This pattern was essentially observed in the first patient (Table I) Unfortunately a satisfactory wedge pressure could not be obtained from the right upper lobe in the second patient but the mean right lower lobe wedge pressure *(from the normally draining segment) does correlate well with the left ventric ular end diastolic pressure* Similar findings *have been previously reported in a few patients* with PAPVC associated with mitral stenosis with intact atrial septum In all the above exam ples the anomalously connected vein functioned as *a safety valve resulting in pathophysiologic* resemblance to Lutembacher s syndrome How ever the pattern of pulmonary flow and resis

tance characteristics described in this combination of lesions appears to be variable and there are at least three examples reported where the pulmonary capillary wedge pressures of the abnormally draining lung were increased to the same extent as those in the normally draining lung in patients with PAPVC mitral stenosis and intact atrial septum.[7, 28] The possible mechanisms for this discrepancy were recently reviewed by Singh and associates.[28]

The echocardiograms of both patients were instructive and deserve further comment. The anomalous pulmonary venous connection (partial or total) leads to volume overload of the right ventricle (RVO). The characteristic echocardiographic features of isolated RVO include increased right ventricular dimension associated with abnormal (paradoxic) ventricular septal motion. The ventricular septal motion of both our patients was completely normal however. This was not unexpected since in addition to RVO both had associated severe volume overload of the left ventricle (mitral regurgitation). It has been pointed out that the expected echocardiographic features of isolated RVO are modified when significant volume overload of both ventricles coexists. Thus the echocardiograms were of no particular help in the detection of right ventricular volume overload in our patients.

From the surgical standpoint the management of the mitral lesion in each case was influenced by the assessment of the valve at the time of operation. In case 1 suture of the congenitally cleft anterior mitral leaflet clearly produced a very satisfactory hemodynamic result but attempted plastic repair of the mitral valve in the second case was inadequate and valve replacement was necessary. Blood from the anomalously connected right pulmonary veins (draining the whole of the right lung in case 1 and only the right upper lobe in case 2) to the superior vena cava was readily directed through a surgically created interatrial communication to the left atrium by means of a pericardial tunnel. There has been no clinical evidence of superior vena cava obstruction at subsequent follow up. There are reports of this having been a problem particularly when concomitant enlargement of the superior vena cava at the proximal end of the pericardial tunnel has not been performed.

Unless there are radiologic grounds for suspecting a regional increase in pulmonary flow any clues to the diagnosis of PAPVC tend to be obscured by severe mitral regurgitation when this is also present. If cardiac catheterization confirms the presence of a left to right shunt serial double sampling indocyanine green dye curves will allow for both localization of the site of anomalous pulmonary venous drainage and quantitation of shunt size (Fig 7). Pulmonary angiography is however invariably necessary for accurate anatomic detail.

Summary

The association of partial anomalous pulmonary venous connection with intact atrial septum and isolated severe nonrheumatic mitral regurgitation is rare this combination of lesions having been reported on only one other occasion. Two such cases have been presented with each patient having experienced an episode resembling subacute bacterial endocarditis. At operation however the mitral valve had a congenital cleft in one case and was normal in the other. One patient underwent mitral valvuloplasty and the second patient had mitral valve replacement. The diagnosis of associated partial anomalous pulmonary venous connection was established at cardiac catheterization and successful surgical correction was achieved in each case by diversion of the anomalous pulmonary venous drainage to the left atrium via a pericardial tunnel through a surgically created atrial septal defect.

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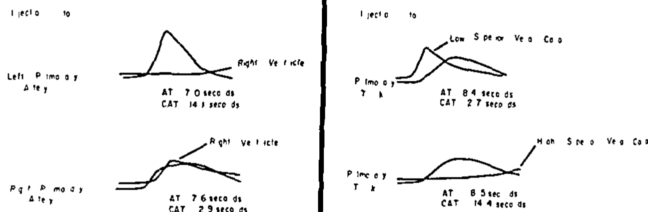


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a = atrial v = ventricular m = mean

severe mitral regurgitation of recent onset Although ruptured chordae tendineae might be expected in this situation at surgery all chordae tendineae were intact and the mitral leaflets were soft and pliable There was no stigma of rheumatic fever or bacterial endocarditis This was of particular interest as successful management of this entirely unexplained mitral regurgitation could be achieved only by mitral valve replacement Postoperatively this patient remains symptomatic and it cannot be excluded that he may have some form of myocardial disease

Comparison of wedge pressures from normally and anomalously draining lung segments has produced interesting observations There have been a number of reports of cases of PAPVC to the superior vena cava or right atrium associated with mitral stenosis and intact atrial septum in which disparate pulmonary arterial wedge pressure recordings from different parts of the same lung have been outlined This difference can be easily understood since the wedge pressure of the anomalously draining segment will reflect the lower right heart pressure This pattern was essentially observed in the first patient (Table I) Unfortunately a satisfactory wedge pressure could not be obtained from the right upper lobe in the second patient but the mean right lower lobe wedge pressure (from the normally draining segment) does correlate well with the left ventricular end diastolic pressure Similar findings have been previously reported in a few patients with PAPVC associated with mitral stenosis with intact atrial septum In all the above examples the anomalously connected vein functioned as a safety valve resulting in pathophysiologic resemblance to Lutembacher s syndrome How ever the pattern of pulmonary flow and rests

Cor triatriatum Report of case in a young adult with special reference to the echocardiographic features and etiology of the systolic murmur*

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Cor triatriatum is an unusual congenital malformation in which a fibromuscular membrane divides the left atrium into a posterosuperior chamber receiving the pulmonary veins and an anteroinferior chamber in communication with the left ventricle through a normal mitral valve Usually there is a single central defect in the fibromuscular membrane but rarely there may be more than one defect The pathophysiology of this malformation includes pulmonary venous and pulmonary arterial hypertension with secondary right ventricular hypertrophy

The occurrence of the lesion in the adult has been described in several reports Surgical correction following hemodynamic and angiographic recognition of the lesion has recently been emphasized Systolic diastolic and continuous murmurs have been described in association with cor triatriatum The association of the systolic murmur with flow across the intra atrial membrane was first *suggested* by McGuire and co workers The echocardiographic *features* of cor triatriatum have been briefly *reported in* infants and children and reports exist of such findings in an adolescent and in a young adult

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Th op ons asserti on c tained h rein are those f th thors nd are ot to be con *trued as* off cial a r flect g th views of the Navy Departm nt r th Na l Service t l rg

The present report describes a 19 year old woman with cor triatriatum documented by hemodynamic and angiographic studies A systolic murmur was noted *preoperatively* but *not* during the postoperative period Echocardiographic abnormalities compatible with *an* intra atrial membrane were also *noted preoperatively* but not following surgical excision of the membrane

Case Report

A 19 year old woman was admitted for evaluation of hemoptysis of recent onset The patient was the product of a normal pregnancy and had been in excellent health until five months prior to admission when she experienced a syncopal episode while *playing Frisbee She noted* dizziness and presyncope with effort *during the next four months* Four weeks prior to admission the patient experienced *orthopnea* wheezing and hemoptysis for two days These symptoms *abated with* the u e of two pillows There was no history of pelvic sepsis *thrombophlebitis* or acute rheumatic fever Her only medica*tion was oral* contrac ptives

On physical examination her blood pressure was 110/"0 The heart *rate was* 7 and regular The venous pressure demonstrated a dominant "a" wave The carotid pulsations were normal The chest was *resonant and* clear The left ventricular impulse was *normal A prominent* right ventricular impulse was present at *the left sternal edge* The first heart sound was of normal *intensity The* second heart sound split physiologically with an *accentuated* pulmonic component No gallop sounds were noted A Grade III/VI crescendo late systolic murmur *loudest* at the apex increased in intensity with inspiration (Fig 1) The remainder of the physical examination was normal

A posteroanterior *chest* roentgenogram demonstrated a normal cardiothoracic *ratio* (Fig 2) There was distribution of pulmonary blood flow to the *upper* lobes A left atrial double density was not noted and the left atrial appendage was not enlarged *A lateral* chest roentgenogram demonstrated right ventricular *enlargement* (Fig 2) The electrocardiogram demonstrated normal sinus *rhythm* right axis deviation of

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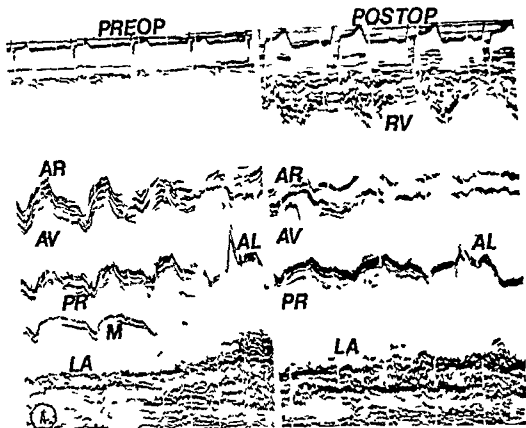


Fig 3A and B A Preoperative echocardiogram demonstrating the membrane in the left atrium AR = anterior aortic root AV = aortic valve PR = posterior aortic root AL = anterior mitral leaflet M = intra atrial membrane LA = left atrium B Postoperative echocardiogram recorded in the same position is normal following surgical resection of the membrane RV = right ventricle AR anterior aortic root AV = aortic valve PR = posterior aortic root AL = anterior mitral leaflet LA = left atrium

radiolucent membrane (Fig 4) The right ventriculogram demonstrated no tricuspid regurgitation

The patient underwent excision of the intra atrial membrane under cardiopulmonary bypass Prior to cardiotomy all four cardiac chambers were directly palpated Systolic and diastolic thrills were noted over the left atrium and were not felt over the other cardiac chambers The membrane appeared to be fibromuscular with an irregular central orifice measuring by 15 mm (Fig 5) The mitral valve was normal The postoperative course was uneventful The patient is currently asymptomatic and has no heart murmurs A postoperative echocardiogram recorded using the same technique as employed preoperatively failed to show the intra atrial membrane (Fig 3B)

Discussion

Cor triatriatum is a congenital anomaly ordinarily presenting within the first two years of life Its initial detection in adolescence and adulthood is well documented in the literature Progressive stenosis of the orifice of the intra atrial membrane has been suggested as a possible explanation for the delayed occurrence of symptoms in some patients Fibrosis and thickening of the intra atrial membrane were noted adjacent to the orifice in our patient lending support to the hypothesis that progressive orifice narrowing accounts for the appearance of symptoms in adults

The systolic murmur and the systolic and diastolic thrills noted over the left atrium at the time of surgery are even more intriguing Normal left and right ventriculography excluded atrioventricular valve regurgitation as the genesis of these findings The murmur and thrills were absent immediately following surgery Thus the evidence is overwhelming that blood transiting the orifice of the intra atrial membrane accounted for the murmur and thrills A diastolic murmur was not heard preoperatively and the diastolic thrill was less prominent than the systolic thrill over the left atrium at the time of surgery Accordingly it can be assumed that the gradient and flow across the membrane were

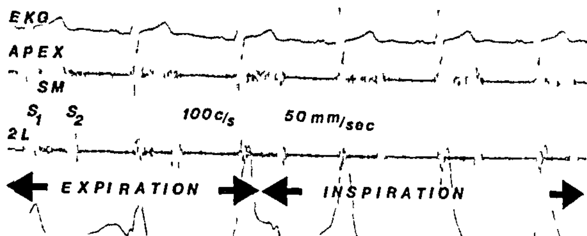


Fig 1 *Phonocardiogram showing inspiratory accentuation of the systolic murmur SM* = systolic murmur S_1 = first heart sound S_2 = second heart sound *2L* = second left interspace *C/S* = cycles per second 50 mm / sec = paper speed



Fig 2 Posteroanterior *(left)* and lateral *(right)* chest roentgenograms showing prominence of the pulmonary artery and the right ventricle redistribution of pulmonary blood flow to the upper lobes and no evidence of left atrial enlargement

+150 degrees prominent R waves in V and S waves in V compatible *with right ventricular hypertrophy The P waves in the inferior* leads were notched but of normal duration The preoperative echocardiogram revealed a normal mitral valve aortic valve *left ventricular size and interventricular septal* motion The right ventricle was enlarged A linear echo which separated *the left* atrium into two chambers was noted parallel *to the posterior* aortic root and approximately midway between it and the posterior wall of the left atrium (Fig 3*A*)

Right and left heart catheterization was performed The mean right atrial pressure was 4 mm Hg (a = 6 v = 4 mm Hg) the right ventricular pressure 50/6 mm Hg the pulmonary artery pressure 50/28 (mean = 35 mm Hg) and the *mean pulmonary wedge pressure was 28 mm Hg* (a = 24 v = 30 mm Hg) The cardiac output was 5 8 L /min the total systemic resistance was 1140 dyne sec cm and *the pulmonary resistance was 100 dyne sec cm Hydrogen circulation* time in the pulmonary artery was normal which excluded any left to right shunt Simultaneous recording of the left ventricular and pulmonary arterial wedge pressures demonstrated a mean diastolic gradient of 23 mm Hg

The left ventriculogram was normal and no mitral regurgitation was present A levophase pulmonary angiogram showed the pulmonary veins draining into a posterosuperior chamber separated from the anteroinferior left atrium by a thin

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Fig 4 Levophase pulmonary angiogram demonstrating a thin radiolucent membrane dividing the left atrium into posterosuperior and anteroinferior chambers *MBR* = membrane *MV* = mitral valve

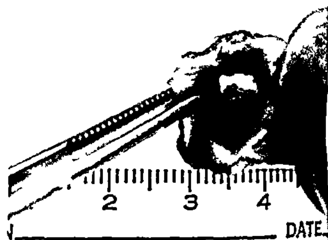


Fig 5 Surgical specimen consisting of the fibromuscular intra atrial membrane and demonstrating an irregular 5 by 15 mm orifice surrounded by the thickened and calcified tissue

greater during systole than during diastole These hemodynamic events presumably explain the presence of the systolic murmur in our patient Accentuation of the murmur during inspiration is not presently understood A murmur of similar quality and behavior with respiration was described in the patient reported by Gibson and associates[1]

The echocardiographic features of cor triatriatum have been described in all age groups [1] These reports have also documented the presence of a linear echo in the left atrium of individuals with cor triatriatum The linear echo patterns illustrated in these reports are of two types one in which the abnormal echo is best recorded either behind or in close association with the mitral leaflet echo[10] and the other in which the abnormal echo is best recorded in the posterior left atrium behind the aortic root Regardless of location the echoes in question have been shown to be in motion The pattern of motion has been variable either paralleling that of the mitral leaflets[1] or posterior aortic wall[9] or showing a pattern of motion out of phase with that of other cardiac structures[9] In our patient as well as in that of Gibson and associates[10] the abnormal echo recorded preoperatively could no longer be demonstrated following excision of the intra atrial membrane This would suggest that this echo originated from the intra atrial membrane

In conclusion cor triatriatum is a surgically correctable cause of pulmonary venous obstruction whose initial detection may be delayed until the adult years It appears that the gradient and flow across the intra atrial membrane are greater during ventricular systole Echocardiographic recognition of this structure will help to establish earlier diagnosis to enable the early institution of corrective surgery

Summary

The clinical angiographic and echocardiographic features of cor triatriatum are described in a young adult A systolic murmur heard preoperatively was palpated over the left atrium at the time of surgery It would appear that murmurs associated with cor triatriatum occur secondary to flow across the intra atrial membrane

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Clinical pathologic conference

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DR SAVITRI SHRIVASTAVA A 5 month old, female infant was born following 36 weeks gestation and normal delivery Since birth, she was tachypneic, particularly during feeding A cardiac murmur was discovered at 2 months of age and she was hospitalized for cardiac evaluation and treatment of congestive heart failure Physical examination revealed an active alert, acyanotic infant weighing 3 76 kilograms The respiratory rate was 60/minute with minimal intercostal retraction and the pulse rate was 150/minute The blood pressure was 80 mm Hg by the flush method in the upper and lower extremities The lungs were clear to auscultation The first cardiac sound was normal and the second cardiac sound showed wide fixed splitting and the pulmonary component of the second sound was accentuated A third heart sound was heard throughout the precordium A long III/VI ejection systolic murmur was heard maximally along the left sternal border and transmitted throughout the precordium and back A Grade III/VI mid diastolic murmur was audible best along the lower left sternal border but was transmitted toward the apex The liver was palpable 2 5 cm below the right costal margin and was smooth and soft The splenic tip was palpable

Laboratory data included serum sodium 141 mEq /L, potassium 5 7 mEq /L pH 7 5 Pco 22 torr the Po was 124 torr while the patient was inspiring 100 per cent oxygen The hemoglobin was 11 4 gm per cent and hematocrit was 35 0 per cent Total leukocyte count was 12 500/mm³ with the differential leukocyte count showing polymorphs 42 lymphocytes 46 monocytes 8 eosinophils 2 and basophils 2 per cent

The electrocardiogram (Fig 1) revealed a frontal plane QRS axis of +120 degrees and right ventricular hypertrophy

The thoracic roentgenogram (Fig 2) showed moderate cardiac enlargement and marked increase in pulmonary vasculature The left atrium was not enlarged The echocardiogram revealed normal intracardiac anatomy Dr Moller will you discuss the differential diagnosis of this case?

DR JAMES H MOLLER This infant presented the cardinal features of congestive heart failure namely, tachycardia tachypnea, hepatomegaly and cardiomegaly In the age of this patient cardiac failure most commonly results from conditions (1) associated with a large left to right shunt at either the ventricular or great vessel level (2) obstructive lesions or (3) myocardiopathies

The loud systolic murmur in this infant suggests a left to right shunt at the ventricular level but there was also a diastolic murmur along the left sternal border indicating a shunt at the atrial level Similar physical findings could also be presented with (1) left ventricular-right atrial communication (2) double outlet right ventricle or (3) endocardial cushion defect The lack of left ventricular hypertrophy on the electrocardiogram and absence of left atrial enlargement on

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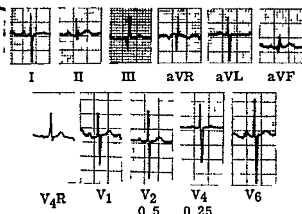


Fig 1 Electrocardiogram of the 5 month old female infant See text for explanation

either the echocardiogram or roentgenogram would favor an interatrial communication It is very uncommon for isolated atrial septal defect to cause congestive heart failure in infants or children unless associated with a left sided cardiac abnormality or a coexistent ventricular shunt

I would therefore favor the view that the presumed atrial septal defect is either associated with some other condition or is part of the complex of the endocardial cushion defect Lack of left axis deviation in the electrocardiogram and echocardiographic recording of normal tricuspid and mitral valves virtually rules out the possibility of endocardial cushion defect

Absence of cyanosis and a Po of 124 tend to rule out admixture lesions like double outlet right ventricle with supracristal ventricular septal defect transposition of the great vessels and single ventricle without pulmonary stenosis Abnormal frontal plane axis may sometimes give a clue to a diagnosis of double outlet right ventricle

The clinical data suggest a left to right shunt both at the atrial and ventricular levels

While the shunt at the ventricular level may be the result of a simple ventricular septal defect special studies are needed either to establish this diagnosis or to identify some other condition such as a left ventricular-right atrial communication or a double outlet right ventricle with a subaortic ventricular septal defect May we see the cardiac catheterization data?

Dr. Shrivastava Cardiac catheterization was performed from the right saphenous vein (Table I) The catheter was passed easily from the right atrium into the left atrium indicating an interatrial communication of some type From the right ventricle the catheter could be passed into the ascending aorta indicating a ventricular septal defect Oximetric data showed a large left to right shunt at the atrial level (71 per cent) and no evidence of a right to left shunt No additional shunt at ventricular level was demonstrated by the oximetric data



Fig 2 Roentgenogram of thorax See text for details

Table I Synopsis of cardiac catheterization data

Site	*Pressure (mm Hg)*	*Oxygen saturation (%)*
Inferior vena cava	–	70
Superior vena cava	–	53
Right atrium	a = 5 v = 3 m = ?	high 73 low 87
Right ventricle	95/0–8	84
Pulmonary artery	9?/25 M = 52	85
Left atrium	a = 7 v = 4 m = 3	95
Left ventricle	105/0–8	95
Aorta	96/50 m = 68	98

Pressure studies revealed identical mean pressures in the two atria suggestive of a large interatrial communication The pressures in the two ventricles were essentially equal The pulmonary arterial pressure was severely elevated (95/25) and since left atrial pressures were normal this would indicate precapillary pulmonary hypertension No gradients were recorded across the tricuspid or pulmonary valves Several angiograms were performed Dr Formanek would you describe these?

Dr Augustin Formanek Initially contrast material was injected into the right ventricle (Fig 3a) A markedly enlarged trabeculated right



Fig 3 *a* Right ventriculogram in frontal view *b* Left ventriculogram in lateral view

ventricular cavity was opacified and the pulmonary valve was normal There was slight opacification of the left ventricle presumably through a ventricular septal defect During the levophase of the right ventriculogram, a normal sized left atrium was visualized and subsequently there was slight opacification of the right atrium through an atrial septal defect

A left ventriculogram was also performed (Fig 3*b*) The catheter passage into the left ventricle *seemed to occur in an unusually low position in* the atrial septum as is present in patients with endocardial cushion defect Following opacification of a normal sized left ventricular cavity the right ventricle was opacified through an infracristal ventricular septal defect The great vessels were normally related and the two semilunar valves were normally positioned The left ventricular outflow tract was normal

An aortogram revealed a normal aorta

DR MOLLER Thank you Dr Formanek

The data presented establish the diagnoses of *atria septal and ventricular septal defects and* exclude the other conditions which I mentioned

DR SHRIVASTAVA In spite of adequate digitalization the congestive heart failure increased in degree and the patient did not gain weight Therefore *corrective operation was advised and* undertaken when the patient was 5 months of age Dr Nicoloff, would you please describe the operative findings?

DR DEMETRE M NICOLOFF In approaching the heart we found no *left innominate* vein but found a persistent left superior vena cava which appeared to drain into either the left atrium or the coronary sinus Upon opening the right atrium, an atrial septal defect was not seen *although a small patent foramen ovale* was present The orifice of the coronary sinus was markedly enlarged and was thought to be the result of drainage of the left superior vena cava into the coronary sinus To establish this a probe was passed through the coronary sinus ostium Our inability to pass a probe into the left superior *vena cava through this route was interpreted* as being caused by a peculiar angulation of the venous structures Upon opening the right ventricle a large ventricular septal defect was found and closed by the placement of a Dacron patch The heart assumed normal function upon completion of the operation In the immediate postoperative period, hyperpyrexia pulmonary infiltrates persistent nodal tachycardia and hypotension developed Treatment included administration of antibiotics dilantin and other supportive therapy Improvement did not occur *and the patient died on the second* postoperative day

DR SHRIVASTAVA The significant findings at autopsy were confined to the heart and lungs The heart was markedly enlarged and showed a *prominent right ventricular outflow tract* The great vessels were normally related with the pulmonary trunk being somewhat wider than the ascending aorta The right atrium was dilated The foramen ovale displayed a valvular competent patency At the anticipated location of the coronary sinus ostium lying inferior to the



Fig 4 *a* Right atrium *(RA)* and right ventricle *(RV)* The probe is in a valvular competent foramen ovale At the anticipated location of the coronary sinus ostium is an atrial septal defect *(ASD)* *IVC* = inferior vena cava *L* = liver *b* Right ventricle *(RV)* Patch *(D)* representing recent closure of a ventricular septal defect Right ventricular hypertrophy

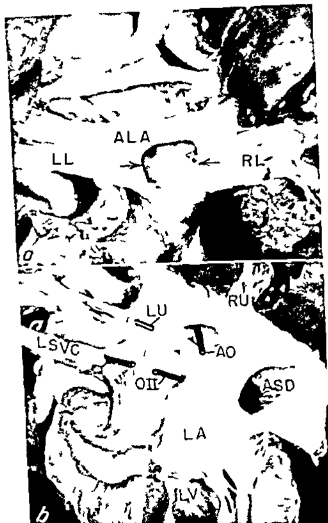


Fig 5 *a* Upper segment of left atrium *(ALA)* viewed from above receiving left and right lower pulmonary veins *(LL RL)* Opening *(between arrows)* in lower part of chamber communicated with main part of left atrium below *b* Lower part of left atrium *(LA)* and a portion of left ventricle *(LV)* Atrial septal defect *(ASD)* in posteroinferior portion of atrial septum Left upper and right upper pulmonary veins *(LU RU)* join this portion of left atrium as does the left superior vena cava *(LSVC)* Probe labelled *OII* is in interatrial ostium II of valvular competent foramen ovale Probe labelled *AO* is in communication between main body of left atrium portrayed here and overlying accessory left atrial chamber shown in *a*

foramen ovale was a large atrial septal defect (2 0 by 1 5 cm) The coronary sinus was absent (Fig 4*a*) A left superior vena cava was present and terminated in the left atrium near the base of the atrial appendage At 1 0 by 1 0 cm Dacron patch closed on infracristal ventricular septal defect (Fig 4*b*)

The left atrium was hour glass shaped the narrow zone being relatively wide and separating the left atrium into two segments The upper segment received the lower pulmonary veins of each side while the lower segment received the upper pulmonary veins and the left superior vena cava The openings of the atrial appendage inter atrial ostium II and mitral valve were in the lower segment (Fig 5)

The walls of both ventricles were of near equal thickness The aortic arch was left sided and showed normal branching The valves were normal as were the coronary arteries of which the posterior descending branch across from the left circumflex artery

The lungs were congested grossly Histologic

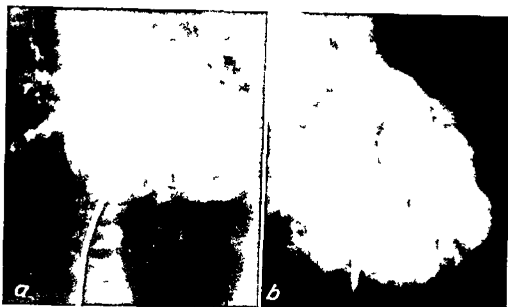


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Pitfalls and limitations of M mode echocardiography

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Echocardiography is an accepted diagnostic *procedure in clinical and investigative cardiology* The expanded application of the noninvasive technique is in a phase of development and problems in instrumentation and interpretation still persist As with any new and promising technique an impressive volume of information has been accumulated but along with this exciting growth and development technical problems and inconclusive findings have sometimes dampened our initial enthusiasm Regrettably, even published recordings are of such poor quality that interpretation has been erroneous and misleading Much more information is needed to determine false positive and false negative results for even accepted diagnostic criteria It is essential to know whether echocardiography is superior or inferior to older noninvasive procedures in the diagnosis of common cardiac conditions Echocardiography must be correlated with findings obtained by cardiac catheterization observations at the time of surgery and at necropsy Larger and long term prospective studies will help clarify these problems

We have recognized many of these problems in our laboratory and wish to expand on some of the pitfall of technique and interpretation

Interventricular septum

Hagan and associates have shown that the upper one third of the septum moves anteriorly during systole (similar to anterior aortic wall motion) and that the septum has a pivoting type of motion usually at the junction of its upper one third and lower two thirds The lower two thirds of the septum moves posteriorly during systole (normal septal motion) Motion beyond the pivoting point is a posterior motion and the upper one third of septum acts as a hinge for the lower two thirds Thus in order to differentiate normal from paradoxic septal motion it is necessary to scan the entire interventricular septum from aortic root to apex and to evaluate septal motion below the plane of the mitral valve

There are numerous disorders associated with abnormal septal motion These include congenital abnormalities such as secundum atrial septal defect ostium primum septal defect partial and total anomalous venous drainage Ebstein s anomaly [9, 10] and congenital absence of pericardium [1] Acquired causes include right ventricular volume of any cause such as pulmonary hypertension with functional tricuspid insufficiency pulmonic insufficiency coronary artery disease [1] severe left ventricular dysfunction [1] constrictive pericarditis and the result of open heart surgery for aortic and mitral valve replacement [1] Although septal motion is abnormal in patients with LBBB RV pacemakers and with PVC s arising from the right ventricle the pattern of motion is slightly different from that of right ventricular volume overload of any cause There is a distinctive early systolic posterior movement of the septum occurring within 0 04 second of the onset of the QRS followed by a subsequent anterior motion reaching maximal excursion 360 msec after QRS Normal or intermediate septal motion has been observed in six of 16 patients studied with LBBB in our laboratory Paradoxical septal motion loses its

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examination of the lungs showed congestion and medial hypertrophy of the muscular arteries and arterioles

Dr Edwards would you please comment on the findings in this case?

DR JESSE E EDWARDS The basic condition present in this case conforms to that described from our laboratories in 1965 by Raghib and associates[1] as a developmental complex consisting of three abnormalities namely (1) termination of the left superior vena cava into the left atrium (2) absence of the coronary sinus and (3) atrial septal defect The atrial septal defect is in a peculiar position lying in the posteroinferior angle of the atrial septum From the right atrial aspect the defect lies in the position of the coronary sinus ostium when a coronary sinus is present Lying in this position the defect may be confused with an enlarged coronary sinus ostium

While this complex may appear without other associated anomalies some may be present

Of five autopsied cases described in the original report three showed ventricular septal defects Of these two were part of associated endocardial cushion defect When the latter condition is associated it is of interest that the atrial septal defect of the endocardial cushion defect and that of this complex coalesce This yields an unusually large atrial septal defect

It is of interest that, although the left superior vena cava joined the left atrium, no systemic arterial desaturation was noted This may be explained by the large volume of pulmonary flow incident to the presence of the atrial and ventricular septal defects coupled with the possibility that some of the blood entering the left atrium through the left superior vena cava had been swept through the atrial septal defect

FINAL DIAGNOSES Complex of absence of coronary sinus atrial septal defect, and left superior vena cava joining left atrium associated with ventricular septal defect

REFERENCE

1 Raghib G Ruttenberg H D Anderson R C Amplatz K Adams P Jr and Edwards J E Termination of left superior vena cava in left atrium atrial septal defect, and absence of coronary sinus A developmental complex Circulation 31 806 1965

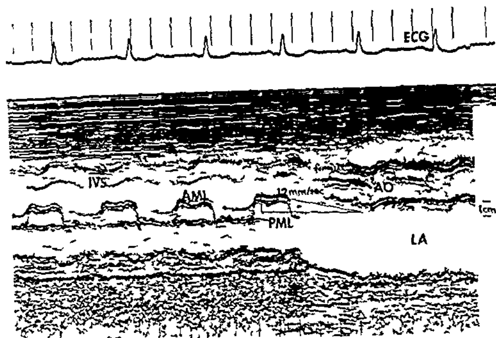


Fig 1 Echogram of a patient with rheumatic heart disease and aortic and mitral insufficiency No dia tolic gradient across the mitral valve was demonstrated The diastolic closure slope of the anterior mitral leaflet is markedly reduced measuring 12 mm /sec and there is thickening of the anterior leaflet The left atrium is also enlarged Abbreviation *AO* = aorta *PML* = posterior mitral leaflet *AML* = anterior mitral leaflet *IVS* = interventricular septum *LA* = left atrium

useful in the mixed lesion and generally the mitral valve echogram resembles that of mitral stenosis even when the stenosis is minimal In addition the mitral valve echogram may demonstrate features of mitral stenosis although the patient may show clinical and hemodynamic evidence of pure mitral regurgitation (Fig 1)

Rupture of the chordae tendineae

Numerous echocardiographic criteria for the diagnosis of ruptured chordae tendineae of the posterior leaflet of the mitral valve have been reported Generally posterior leaflet chordal rupture has been recognized by an early systolic plunge of the leaflet to the posterior left atrial wall during systole followed by anterior motion at the onset of diastole In addition to the characteristic posterior mitral valve motion other echocardiographic features are suggestive but not diagnostic of chordal rupture These include excessive systolic motion of the left atrial wall normal left atrial size and marked systolic motion of the interventricular septum Multiple linear echoes with the left atrial chamber thought to be echoes of the flail posterior leaflet may be mistaken for left atrial thrombi or may be artifactual

With the use of exploratory continuous sector scan echoes recorded from within the left atrial cavity which eventually blend into those from the posterior leaflet of the mitral valve confirm the diagnosis of a flail posterior leaflet On occasion multilayered pattern of diastolic echoes may be detected behind the mitral valve in patients with posterior chordae rupture This pattern may be indistinguishable from atrial myxoma

Rupture of the chordae tendineae to the anterior mitral valve leaflet is somewhat more difficult to diagnose echocardiographically than rupture of those of the posterior leaflet The echocardiographic criteria of a flail anterior leaflet include marked erratic diastolic fluttering increased amplitude of motion of the anterior mitral leaflet increased amplitude of motion of the interventricular septum with normal posterior wall motion normal or slightly enlarged left atrium and exaggeration of motion of the posterior left atrial wall during systole Utilizing exploratory continuous scanning technique movement of the anterior leaflet of the mitral valve into the left atrium during systole may be demonstrated Diastolic fluttering of the anterior leaflet of the mitral valve has been observed in patients

specificity since so many disorders are associated with abnormal motion and therefore, abnormal septal motion must be interpreted in light of *the clinical setting* Abnormal septal motion also has recently been observed in a normal subject [0] In *contrast normal* septal motion does not exclude a small left to right shunt at the atrial level [1]

Mitral stenosis

The echocardiographic features of mitral stenosis include *reduced diastolic closure slope (E F)*, thickened mitral valve leaflet, reduced "a" wave amplitude and increased systolic closure slope The amplitude of motion of the mitral valve leaflet from its point of closure (C) to its full open position (E) and the opening velocity (DE) are indicators of the pliability of the mitral valve

The major usefulness of echocardiography in evaluating patients with mitral stenosis has been a reduction in the early diastolic closure slope of the anterior mitral leaflet and anterior motion of the posterior mitral leaflet Recently doubt has been cast on the specificity of these two observations

Several investigators have shown good correlation between the diastolic slope and the mitral valve area as estimated at surgery or necropsy However a recent study by Cope and colleagues comparing the E F slope on the echocardiogram and the calculated mitral valve area in 61 patients revealed a poor correlation ($r = 0.51$)

By combining their data with the data from other studies, 127 out of 210 patients with severe mitral stenosis had an E F slope of < 15 mm / sec i e the sensitivity was 60 5 per cent Of 170 patients with an E F slope of < 15 mm /sec 120 had severe mitral stenosis with a specificity of 75 per cent Based upon their observations Cope and colleagues concluded that the E F slope of the anterior mitral leaflet is in general an unreliable index of the severity of mitral stenosis in the individual patient They *also demonstrated that* patients with decreased amplitude of excursion showed no correlation between valve area and slope and that the size of the orifice is undependent of the movement of the valve

Patients with reduced ventricular compliance or primary pulmonary hypertension have reduced diastolic closure slope of the anterior mitral *leaflet* [11] The importance of the normally moving posterior mitral leaflet in differentiating these patients from patients with mitral stenosis has been stressed [31] Duchak and co workers[14] first emphasized the importance of the anterior motion of the posterior mitral leaflet paralleling the anterior mitral leaflet in patients with mitral stenosis However, Levisman and associates found that the posterior mitral leaflet moved posteriorly in 16 of 167 patients Generally these patients had milder mitral stenosis however in five of the 16 patients with severe mitral stenosis *the motion of the posterior leaflet was normal*

Thus the characteristic echocardiographic features must be evaluated in the clinical setting For the individual patient the echocardiogram may provide misleading information especially when *only the E F slope* and motion of the posterior mitral leaflet are considered However when the characteristic echocardiographic findings are present in the patient presenting with the clinical manifestations of mitral stenosis useful information can be obtained Multiple discrete linear echoes or amorphous thick conglomerate echoes within the mitral valve complex suggest *significant calcification In such a setting* mitral valve replacement should be considered Assessing the size of the left ventricular outflow tract left ventricular function, size of left atrium and size of right ventricle and pulmonary valve motion are useful parameters in assessing the severity of mitral stenosis degree of pulmonary hypertension function of the left ventricle and *type of prosthesis required*

Mitral restenosis can be diagnosed by serial echocardiography after commisurotomy

Mitral regurgitation

The diagnosis of rheumatic mitral regurgitation cannot be made reliably by echocardiography [1] In most patients with rheumatic mitral regurgitation the amplitude of the mitral valve is increased and an increased E F slope has been reported [1] There may be some overlap with *normal values and these findings generally* have not been regarded as specific and highly diagnostic of mitral regurgitation The finding of both increased *leaflet* thickness and anterior *motion* of the mitral valve in diastole is suggestive of rheumatic mitral regurgitation In patients with combined mitral stenosis and regurgitation the mitral valve echogram shows a rapid initial E F segment followed by a plateau [1] Nanda and associates have not found this pattern to be

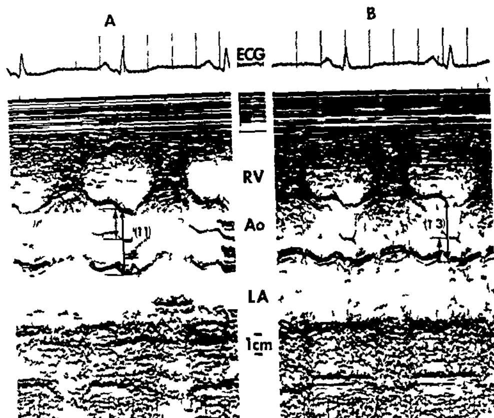


Fig 3 *Panel A* shows normal centrally located diastolic leaflets of the aortic valve with a normal eccentricity index There is minimal fluttering of the aortic leaflets *Panel B* shows the same patient with a different transducer angulation howing that the leaflets are eccentrically placed with an eccentricity index calculated to be 1 3 For determination of eccentricity index see text Abbreviations *RV* = right ventricle *AO* = aorta *LA* = left atrium

that the beam strikes the mitral valve vertically [8] Both leaflets could not always be recorded with this technique

The 47 per cent prevalence of mitral valve prolapse among progeny appears excessively high but nevertheless the findings of Weiss and colleagues and others [4] suggest that this disorder occurs as an autosomal dominant mode of inheritance We believe that the high incidence of mitral valve prolapse detected by echocardiography may indeed reflect problems with technique (Fig 2) Nevertheless echocardiography appears a reliable means of confirming the diagnosis of mitral valve prolapse in patients with isolated non ejection clicks and/or late systolic murmurs

Echocardiographic features of tricuspid valve prolapse are similar to those that have been described in patients with mitral valve prolapse However the tricuspid valve is much more difficult to visualize by echocardiography than the mitral valve unless the right ventricle is dilated

Aortic valve

The normal aortic valves are depicted echocardiographically within the aortic root as thin cusp echoes producing a box like configuration during systole and a central line during diastole Fine systolic oscillations of the aortic valve cusps may be recorded in normal individuals Left ventricular ejection time can be measured from the point of opening of the aortic cusps to the point of closure

Bicuspid aortic valve Nanda and co workers[5] have described the echocardiographic features of aortic stenosis associated with a bicuspid aortic valve They demonstrated marked eccentricity of the aortic valve cusp echoes in diastole Employing an Eccentricity Index (½ aortic lumen diameter/minimum distance of the diastole echo from the nearest aortic margin) they were able to

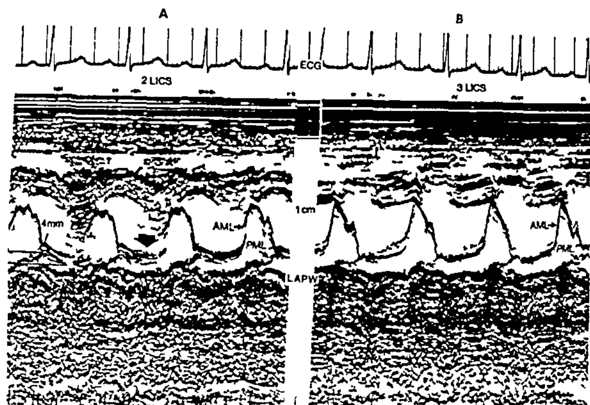


Fig 2 *Panel A* demonstrates false mitral valve prolapse (hammock appearance) in a normal subject The transducer is placed in the second intercostal space (*2LICS*) and is angulated in an excessive inferior direction *Panel B* demonstrates no evidence of prolapse in the same subject when the transducer is placed in the third intercostal space (*3LICS*) Abbreviations *AML* = anterior mitral leaflet *PML* = posterior mitral leaflet *LAPW* = left atrial posterior wall

with aortic insufficiency and in atrial flutter or fibrillation In flail anterior leaflet the vibrations are coarser and more erratic than those observed in patients with aortic insufficiency However coarse erratic vibrations have been seen in patients with chronic aortic insufficiency and the mitral valve echogram alone may not be helpful in differentiating the two conditions

Mitral valve prolapse

The echocardiographic criteria for mitral valve prolapse have been defined by several groups of investigators Diagnostic echocardiographic criteria of mitral valve prolapse include midsystolic buckling or abrupt posterior motion of the posterior mitral valve leaflet and frequently the anterior leaflet as well pansystolic hammock like posterior motion of the valve leaflets with the most posterior displacement of the leaflets greater than 3 mm from the C point In addition, other criteria include persistent posterior motion of the mitral valve leaflets posterior to the C point throughout systole with associated increased mitral valve excursion and multiple leaflet echoes

On the basis of these echocardiographic criteria the incidence of mitral valve prolapse has been reported to range between 6 and 12 per cent Low amplitude anterior systolic motion of the mitral valve similar to that seen in idiopathic hypertrophic subaortic stenosis has been reported Valsalva maneuver or amyl nitrite do not increase the systolic anterior motion in patients with mitral valve prolapse in contrast to those patients with idiopathic hypertrophic subaortic stenosis Rarely fluttering of the systolic portion of the valve has been demonstrated in patients with prolapse of the mitral valve in association with bacterial endocarditis

Using a modified echocardiographic technique which avoided excessive inferior angulation of the transducer Weiss and associates reported an incidence of 47 per cent in 57 first degree relatives of 17 propositi However if excessive inferior transducer angulation was employed particularly when the transducer was placed in second or third left interspaces the incidence increased to 65 per cent among the first degree relatives and was also found in 83 per cent of normal subjects Ideally the transducer should be placed in the fourth interspace angulated slightly medially so

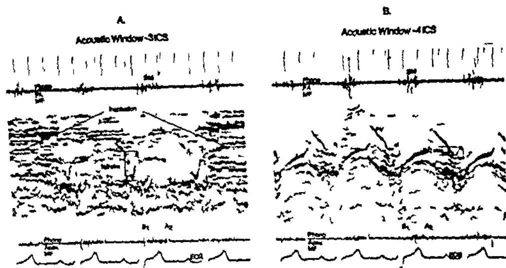


Fig 5 Pulmonary valve echogram from a patient with proved pulmonary stenosis and a gradient of 50 mm Hg across the pulmonary valve *Panel A* shows the transducer in the third intercostal space and the amplitude of A wave motion is 11 mm *Panel B* shows the transducer in the fourth intercostal space in the same patient and the A wave amplitude now measures 5 mm

cm With heavily calcified valves of any etiology marked restriction of aortic valve motion is noted and dense echoes may be recorded in systole and diastole[5] Despite reports claiming that echocardiography can quantitate the degree of aortic stenosis by correlating the degree of valve motion or opening orifices with the valve gradient we believe that the correlation is poor When dense echoes are recorded within the aortic root during systole or diastole excessive calcification or fibrosis of the aortic valve is suggestive without necessarily implying critical stenosis Conversely if thin discrete aortic valves are recorded with a normal valve motion in an elderly patient with an aortic midsystolic murmur significant aortic valvular stenosis can be excluded

Aortic valve orifice size can be affected by cardiac output being decreased in patients with a low cardiac output In congenital aortic stenosis as discussed aortic valve orifice size does not correlate with the degree of stenosis Other indirect echocardiographic parameters may be useful in the assessment of patients with aortic stenosis They include concentric hypertrophy of the left ventricle and decreased diastolic closure slope of the mitral valve Pulmonary hypertension if present can be recognized by the characteristic pulmonary valve motion

Aortic regurgitation The classical echocardiographic features of aortic regurgitation include diastolic fluttering of the mitral valve leaflets[41] diastolic ventricular cavity dilatation[53] and/or wall thickening Mitral valve closure may occur early in *acute* aortic insufficiency because of significant elevation of the left ventricular and diastolic pressure[59] The aortic root size is also helpful in determining the etiology of aortic insufficiency for example in Marfan s syndrome or in cystic medionecrosis the aortic root is markedly enlarged Recently Feizi and colleagues[60] have demonstrated that diastolic separation of aortic valve echoes of more than 1 mm is a useful and important sign of aortic insufficiency This may occur in normal individuals and we have not found this to be a valuable sign in aortic insufficiency

Pulmonary valve

Several echocardiographic techniques for examining the pulmonary valve have been described

The pulmonic valve echoes are frequently recorded incompletely Fig 4 illustrates a normal posterior pulmonic leaflet recorded from different intercostal spaces The a wave reflects the effect of atrial contraction on pulmonic valve motion Point *b* represents the position of the valve at the onset of ventricular ejection The leaflet moves rapidly to point *c* which reflects the valve in a fully open position During systole

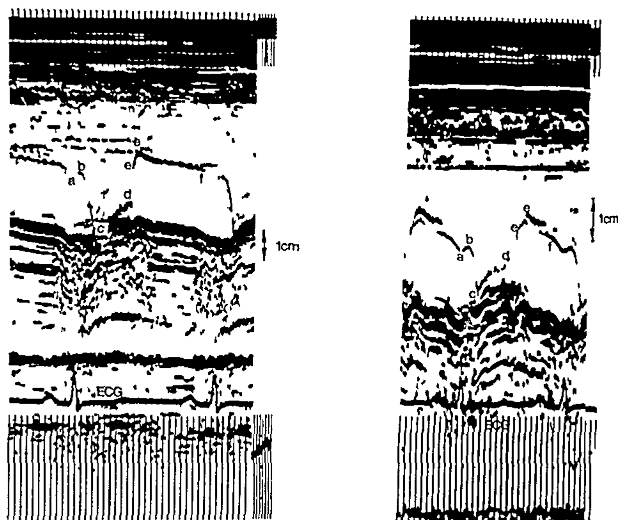


Fig 4 Pulmonary valve echogram in a normal subject *The left hand panel* is in the fourth intercostal space *The right hand panel* is in the third intercostal space These are both from the same patient Points *a b c d e e* and *f* are detailed in the text Notice the varying *e* to *f* slope and the *a* wave amplitude

differentiate subjects with tricuspid valves from those with bicuspid aortic valves Generally patients with bicuspid aortic valves had a high eccentricity index of 1 5 to 1 6 and those with tricuspid aortic valves a low index of 1 0 to 1 25 In approximately half the patients with bicuspid aortic valves multilayered echoes were demonstrated echocardiographically in diastole This finding was present in the absence of fluoroscopic evidence of valvular calcification According to Nanda and colleagues[53] the index was not affected by valvotomy Radford and associates[54] found that an eccentric index of > 1 3 was found in 74 per cent of 31 patients studied with non obstructed bicuspid aortic valves However the central aortic leaflet echoes occurred in the remaining 26 per cent of patients and therefore a normal finding does not exclude a bicuspid aortic valve

The association of a high membranous VSD may result in an eccentricity index of greater than 1 3 despite the absence of an associated bicuspid aortic valve[54] Whether significant aortic valve prolapse is playing a role in these patients is not entirely clear It should be noted that beat to beat variation in eccentricity can occur at onset of diastole as well as varying appearance of multiple diastolic echoes

In one patient with tetralogy of Fallot and a bicuspid aortic valve a normal eccentricity index was recorded Whether the large anterior aortic root and associated VSD is playing a role in producing a false negative result is not entirely clear[54] Thus although eccentricity of the aortic cusps in diastole appears to be specific for a bicuspid aortic valve[53, 54] we have recorded this finding in patients with tricuspid aortic valve and *no* evidence of a VSD (Fig 3) The sensitivity of echocardiography in the diagnosis of bicuspid aortic valve appears to be 75 per cent[54]

Calcific aortic stenosis Mild aortic stenosis as may frequently coexist with rheumatic mitral stenosis is characterized by slight thickening of the valve with restriction of the cusps to about 1 5

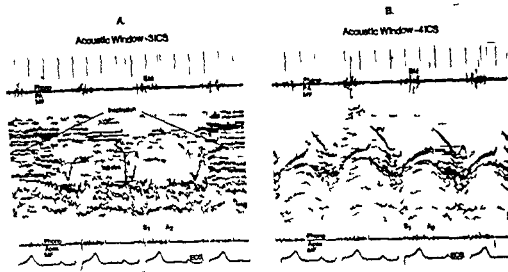


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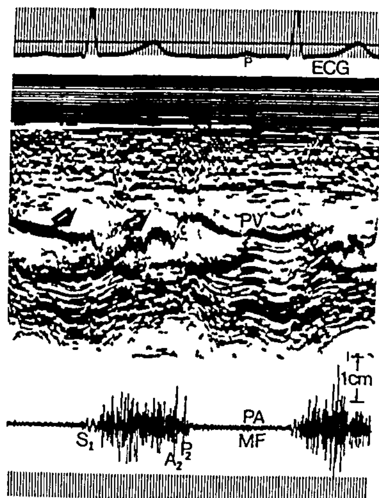


Fig 6 Pulmonary valve echogram in a patient with a subpulmonic VSD Chaotic systolic fluttering (*arrow 2*) of the pulmonary valve is demonstrated *Arrow 1* demonstrates a *decrease in A wave amplitude* Phonocardiogram demonstrates the loud crescendo decrescendo systolic murmur with a widely split second sound (P_2) Abbreviations *PV* = pulmonary valve

there is a gradual anterior movement of the leaflet (*c d*) followed by rapid closure of the valve to the *c* point with diastole Occasionally further anterior motion occurs from point *e* to *e* and may represent transmitted pulsations from the aorta The *e* or *e f* slope represents a gradual posterior motion of the leaflet during diastole Frequently the *b c* slope *c d* slope and diastolic closure *d e* are not well recorded

The normal "a" wave depth recorded during quiet respiration ranged between 2 to 7 mm with an average of 3 7 mm[6] The degree of valvular motion after atrial systole (a wave) increased with *inspiration* However we have observed tremendous variation of the "a" wave depth in normals with measurements up to 7 mm during respiration The amplitude of leaflet motion averaged 13 9 ± 1 8 mm in normal subjects The *e f* slope averaged 36 9 ± 25 4 mm /sec with a range of 6 115 mm /sec[64] In spite of the extreme variable range recorded in normals a low value of 6 mm /sec may still not be regarded as an abnormal finding for the individual patient The mean opening slope (*b c* slope) measured 911 mm /sec[63]

In patients with moderate pulmonary stenosis (gradient greater than 50 mm Hg) the depth of the "a" wave increased markedly to 8 to 13 mm with a mean of 10 mm[6] In addition, the leaflet never returned to a base line or closed position before ventricular systole[6] The exaggerated leaflet motion after atrial systole is probably due to a positive gradient across the valve in end diastole as a result of increased right ventricular end diastolic pressure and force of atrial contraction Note that the "a" wave depth can vary in amplitude depending upon transducer position (Fig 5) It should be noted in patients with gradients of less than 50 mm Hg that the "a" wave depth is frequently normal[6] Thus the echocardiogram is an insensitive tool in the diagnosis of pulmonic stenosis However in the presence of classical findings of moderate to severe pulmonic stenosis, exaggerated "a" wave amplitude of motion with the leaflet never returning to a closed position before ventricular systole is additional confirmatory evidence of pulmonic stenosis

In infundibular stenosis marked chaotic systolic fluttering of the valve leaflet was recorded[63] In one patient with severe infundibular stenosis reported by Weyman and colleagues[65] the "a" wave amplitude was absent the *e f* slope was flat and marked fluttering of pulmonic valve was recorded These findings were indistinguishable from pulmonary hypertension Chaotic systolic fluttering has been noted in our laboratory in patients with sub pulmonic VSD and therefore this finding is not specific for sub pulmonic stenosis (Fig 6) Nanda and associates[66] demonstrated early systolic closure of the pulmonary valve with marked fluttering in the latter part of systole in patients with sub pulmonic obstruction in dextro position of the great vessels

In patients with pulmonary hypertension the "a" wave depth was either absent or measured less than 2 mm[63,64] In addition the *e f* slope was flattened an average of 5 2 mm /sec and sometimes a negative slope was recorded Characteristic features of pulmonary hypertension may be recorded in normal subjects depending upon transducer position (Fig 4) and cycle length

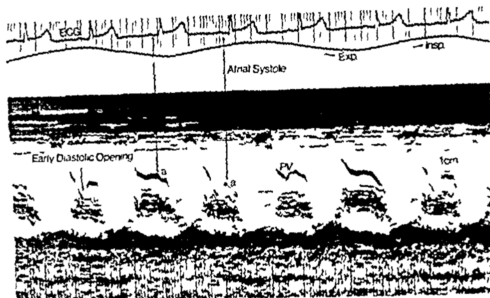


Fig 7 Pulmonary valve echogram from a patient with normal findings at cardiac catheterization Early diastolic opening prior to atrial systole of the pulmonary valve is noted This is clearly evident during inspiration

In atrial fibrillation some of the characteristic features are lost although in most cycle lengths the *e f* is flat Midsystolic closure or notching with or without fluttering was frequently recorded in pulmonary hypertensive patients Occasional large a wave amplitude can occur in pulmonary hypertension in patients with severe right ventricular failure Thus although no one finding is specific for pulmonary hypertension the constellation of the above echocardiographic findings is highly suggestive of pulmonary hypertension and should be interpreted in light of the clinical setting In pediatric patients the classical echocardiographic findings of pulmonary hypertension were not consistently found

In Uhl s anomaly or congenital hypoplasis of the right ventricular myocardium diastolic opening of the pulmonary has been observed [8] The valve opened with atrial systole partially closed and opened again with the onset of ventricular systole Thus in the absence of clinical evidence of pulmonary stenosis a large amplitude of a wave motion may suggest Uhl s anomaly

Weyman implied that while diastolic opening of the pulmonic valve following atrial systole occurs in pulmonic stenosis atrial septal defect and complete heart block rupture of sinus of Valsalva into right atrium was the only cause in which pulmonic valve opening has been observed to precede atrial contraction and was specific for an aorta cardiac fistula We have observed diastolic opening of the pulmonary valve in normal subjects (Fig 7)

Cavity dimensions and wall thickness

Left atrial size The left atrial size can readily be determined by echocardiography Although several investigators have measured the size of the left atrium by different methods [9] [2] we prefer to measure left atrial dimension in early diastole from the damped portion of the record The exact measurement of left atrial dimension is obtained by measuring the distance in millimeters from the strongest posterior aortic wall echo to the posterior left atrial wall Note that varying left atrial dimensions can be obtained in the same subject depending on transducer position and angulation (Fig 8) In addition marked discrepancy between the left atrial size using the suprasternal approach as compared to the left sternal approach can be obtained in any one individual Linear paralleling or punctate echoes are frequently observed within the left atrial cavity and can be frequently mistaken for left atrial clots or tumor The exact mechanism of production of these echoes is obscure Clear cut echocardiographic evidence of left atrial clot is seldom encountered. Most intra atrial thrombi are in the left atrial appendage and not in the path of the transducer beam The thrombi may be adherent to posterior left atrial wall or the thrombus may have embolized at the time of study making

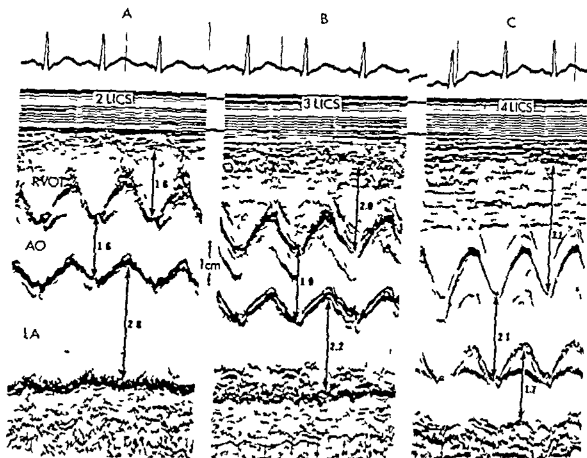


Fig 8 *Varying size of the left atrium and right ventricle depending upon transducer position in a normal subject* *Panel A* demonstrates that when the transducer is in the second left intercostal space the left atrium measures 2.8 cm as compared to the aortic root and right ventricular cavity dimension of 1.6 *Panel B* shows the transducer in the third left intercostal space with a left atrial diameter of 2.2 cm an aortic root of 1.9 cm and a right ventricular cavity dimension of 2.0 cm When the transducer is in the fourth left intercostal space the left atrial size is 1.7 cm *the aortic root size is 2.1 cm and the right ventricular cavity is 3.1 cm* Abbreviations *RVOT* = right ventricular outflow tract *AO* = aorta *LA* = left atrium

detection by echocardiography difficult [73]

In a recent study by Henry and colleagues [74] the presence or absence of atrial fibrillation has been found to correlate with the degree of left atrial dilatation in patients with mitral stenosis aortic stenosis and asymmetric septal hypertrophy Atrial fibrillation was rare when left atrial dimension was below 40 mm but was common when the left atrial dimension exceeded 40 mm [74]

In normal newborns and infants the ratio of the left atrium to aorta is less than 1.0 (0.86 ± 0.10) The left atrium enlarges in patent ductus arteriosus and in this disorder the left atrial/aortic ratio has been reported to be 1.28 [7]

Right ventricular cavity size Estimation of right ventricular cavity size by echocardiography is unpredictable and unreliable unless the right ventricular cavity is grossly enlarged Depending upon transducer position or angulation the size of the right ventricle can vary considerably in any one individual (Fig 8) Positioning the patient in the left lateral decubitus position produces a larger right ventricular dimension than does positioning him in the standard supine position

Aortic root Several investigators [1, 6, 7] have reported different values for the normal echocardiographic measurements of aortic root diameter Measuring the internal aortic root diameter at end diastole Francis and associates reported measurements ranging from 17 to 33 mm (mean of 23.7 mm) in 159 normal subjects The mean aortic root diameter was slightly larger in men than in women

Aortic root dissection The original criteria for the echocardiographic recognition of aortic root dissection included [1]

1 Widening of the anterior aortic walls and/or posterior aortic wall (16.60 to 21 mm anterior wall and 10 to 13 mm posterior wall)

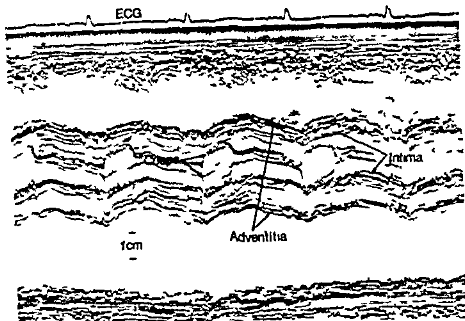


Fig 9 Increased wall thickness in a patient with marked atherosclerosis of the ascending aorta There is significant separation between the inner and outer walls of the anterior and posterior aortic walls that simulates an aortic dissection The aortic cusps are clearly seen

2 Parallel motion of the separated margins of the aortic root walls

3 Enlargement of the aortic root (42 mm or more)

Additional findings included pericardial effusion and diastolic fluttering of the mitral valve Not all patients with dissecting aneurysm may exhibit the classical findings and Brown and colleagues demonstrated the three classical echocardiographic features of aortic root dissection in five of 10 patients without clinical findings of aortic root dissection or aortic valve disease Varying transducer position in relation to membranous ventricular septum and fibrous aortic root-mitral junctures may account for this phenomenon False positive separation of margins of the aortic root walls may be recorded in patients with increased thickness of aortic walls as in atherosclerosis (Fig 9) In addition we have observed normal aortic root recordings in patients with proven Type I aortic dissecting aneurysms

Left ventricular wall motion Despite the numerous earlier reports confirming the reliability of posterior wall velocity as an index of left ventricular contractility a recent report has cast doubt on this assumption Neither maximum nor mean posterior wall velocity is an accurate measure of total ventricular performance in patients with coronary artery disease In the presence of other segmental areas of asynergy the motion of the left ventricular posterior wall is not representative of the entire left ventricular myocardium as a whole In patients with hypokinetic or akinetic septal motion the posterior left ventricular wall may exhibit exaggerated motion In addition the left ventricular wall motion may be reduced in patients with inferior wall infarction and in patients with coronary artery disease [6] Abnormal posterior wall motion has also been reported in patients who have developed angina during exercise Reduced maximum and mean diastolic velocities below the resting values were recorded in patients with exercise induced angina Kovick and associates measured maximal systolic and diastolic endocardial velocity in patients with muscular dystrophy and found the maximal diastolic endocardial velocity to be consistently reduced For the individual patient caution should be exercised since values of maximal diastolic endocardial velocity in normals and in muscular dystrophy patients may overlap In our laboratory we do not measure maximal or mean systolic or diastolic endocardial velocity since we have not found

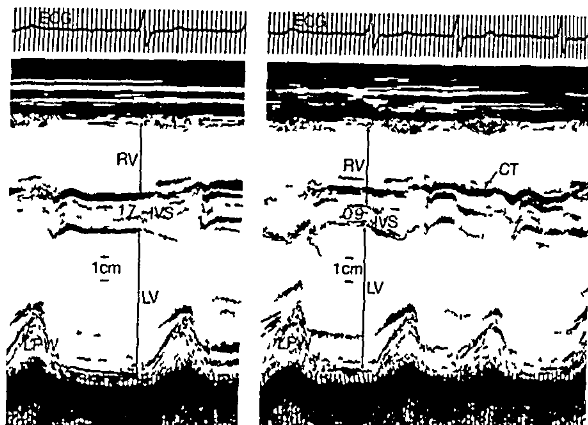


Fig 10 *The left hand panel* shows how incorrect measurement of the septum can lead to a spuriously thickened ventricular septum *The right hand* panel shows that the structure thought to be the right side of the septum *actually is a chordal structure (CT)* This structure moves anteriorly with systole as compared to the right side of the septum which moves in a posterior direction in parallel with the left side of the septum Abbreviations *RV* = right ventricle *IVS* = interventricular septum *LV* = left ventricle *LPW* = left ventricular posterior wall *CT* = chordal structures

these measurements to be of significant value

A localized area of premature contraction of the left ventricular posterior wall accompanied by paradoxic anterior motion of the interventricular septum has been reported in patients with Type A WPW syndrome[88] The abnormality in posterior wall motion has not been always confirmed by other investigators[89 90]

Left ventricular wall thickness The distance between the posterior left ventricular endocardium and epicardium at end diastole has been used as an index of left ventricular wall thickness[91 9] The upper limit of normal for left ventricular wall thickness is 1 1 cm Wall thickness must not be measured in the region of the posterior papillary muscle since the left ventricular wall measurement would be excessive The measurement should be obtained in the region where posterior chordae or preferably posterior leaflet is clearly seen In concentric hypertrophy the ratio of septal to posterior wall thickness is 1 1[43] On occasion left ventricular posterior wall thickness is markedly thickened as compared to septal thickness

Idiopathic hypertrophic subaortic stenosis—Hypertrophic obstructive cardiomyopathy (HOCM)—Asymmetric septal hypertrophy (ASH)

The echocardiographic features of this disorder have been well described an increased septal to posterior wall thickness ratio (the marker for anatomic asymmetric septal hypertrophy)[93] a hypodynamic septum with a hyperdynamic posterior wall[4] failure of the septum to thicken during systole[5] systolic anterior motion of the mitral valve (SAM), indicative of outflow tract obstruction caused by systolic aposition of the anterior mitral valve leaflet and the septum,[96] a narrow left ventricular outflow tract at the start of systole,[97] diastolic collision of the mitral valve and the septum,[9] a decreased E F mitral valve slope[98] and midsystolic closure of the aortic valve leaflets[99] However these findings alone and in combinations have been described in other conditions

Asymmetric septal hypertrophy is defined as the ratio of septal to free left ventricular wall thickness greater than 1 3 1[93 100 101] Technique is

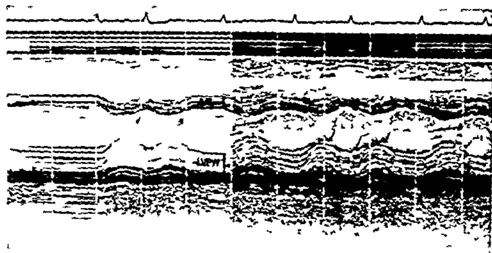


Fig 11A Echogram demonstrating marked thickening of the left ventricular posterior wall (LVPW) measuring 1 8 cm as compared to septal (IVS) thickness which measures 1 0 cm The left ventricular outflow tract is narrowed measuring 2 0 cm

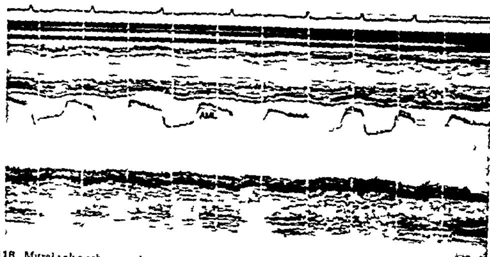


Fig 11B Mitral valve echogram demonstrating markedly decreased diastolic closure slope (E F) of the anterior mitral valve leaflet (AML) simulating mitral stenosis Normal septal thickness is noted (E F slope measures 12 mm/sec)

extremely important and measurement of septal thickness is made at the level when the transducer beam is angulated just below the level of the mitral valve leaflets Left ventricular wall thickness is made at the level where posterior mitral valve leaflet is seen Frequently the right side of the septum is recorded less distinctly than the left side of the septum Because of excessive gain setting or improper angulation of the transducer multiple echoes may be recorded from either side of the ventricular septum This would tend to give the erroneous impression of a thickened septum and the incorrect diagnosis of asymmetrical septal hypertrophy will be made Echoes from the papillary muscle or chordae tendineae of the right ventricle may be mistaken for the right side of the interventricular septum leading to the erroneous impression of a thickened right side of the septum (Fig 10) It should be noted that these structures move somewhat anteriorly during systole whereas the right side of the septum is stationary (Fig 10) or parallels the motion of the left side of the septum

Diagnostic quality echograms cannot be obtained in approximately 10 per cent of patients studied[101] False high or low estimates of wall thickness can occur as a result of inability to delineate one or both of the septal or posterobasal

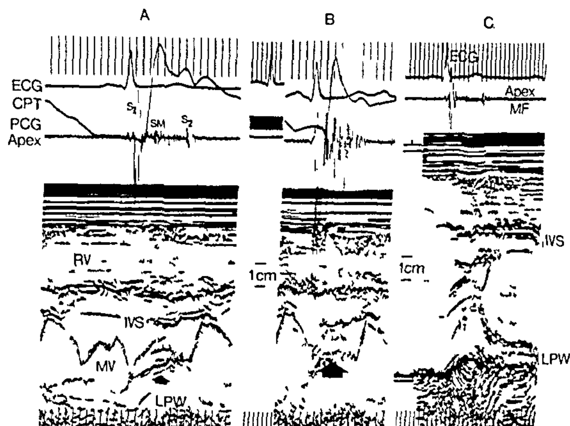


Fig 12 *Panel A* demonstrates simultaneous carotid pulse ECG phonocardiogram and echocardiogram Systolic anterior motion is demonstrated coinciding with the short mid systolic murmur and a bifid carotid pul e *Panel B* demonstrates the response to amyl nitrate with more apparent systolic anterior motion longer systolic murmur and more obvious bifid pulse *Panel C* demonstrates normal ratio of septum and left ventricular posterior wall thickness Abbreviations *RV* = right ventricle *LPW* = left ventricular posterior wall *IVS* = interventricular septum *SM* = systolic murmur

left ventricular wall surfaces On the basis of combined electrocardiographic and echocardio graphic studies idiopathic left ventricular hyper trophy is most unusual[1] The majority of patients with unexplained left ventricular hyper trophy based on electrocardiographic criteria have asymmetric septal hypertrophy as deter mined by echocardiography[1] Shown in Fig 11*A* is the echogram of a 45 year old man with clas sical angina (normal coronary arteriograms) and left ventricular hypertrophy by ECG with normal septal thickness but markedly thickened poste rior wall This patient had no evidence of asym metrical septal hypertrophy or systolic anterior motion but had a narrow left ventricular outflow tract and *reduced mitral diastolic closure slope* (Fig 11*B*) There is a definite need to examine the specificity of asymmetric septal hypertrophy (septum/free wall > 1 3) Asymmetric septal hypertrophy is frequently found in normal newborns and in children with a variety of con genital heart disorders[1,3] In addition dispropor tionate or asymmetric septal hypertrophy has been described in nine of nine patients with primary pulmonary hypertension[104] and in 14 of 30 patients with malignant hypertension[1,5] When the ratio of septal to left ventricular wall thick ness was greater than 1 5 as described by Abbasi and colleagues[11] only three of 14 patients had asymmetric septal hypertrophy

Systolic anterior motion (SAM) has been described in several conditions pericardial effu sion (the SAM disappeared after the effusion was tapped)[1] left ventricular aneurysm,[1] mitral valve prolapse[11] atrial septal defect[11] coronary artery disease (associated with a hypokinetic septum and a hyperkinetic posterior wall but with a normal left ventricular outflow tract and no obstruction)[111] and concentric ventricular *hypertrophy*[11] *An obstruction index relating* the degree and duration of the systolic mitral valve septum aposition has been shown to correlate with the simultaneously measured outflow tract gradient[11] However several reports have docu mented significant SAM and calculated obstruc tion indices without simultaneously measured left ventricular outflow tract gradients[113, 114] In addition we have documented eight cases out of a

total of 81 patients with systolic anterior motion of the mitral valve without asymmetric septal hypertrophy (Fig 12)

The definitive diagnosis of IHSS HOCM ASH has become a function of the echocardiographic laboratory This entity has been divided into four basic types based on echocardiographic findings ASH without SAM (nonobstructive—*a* clinically inapparent or *b* presenting with symptoms) ASH with provocable SAM (*c* provocable obstructive with symptoms) and ASH with constant SAM (*d* constant obstructive with symptoms) If the studies are properly done most patients fit into one of these four categories However a definite minority such as the cases described above cannot be so easily categorized

Pericardial effusion

Echocardiography has been accepted as one of the most sensitive and accurate means of diagnosing pericardial effusion Nevertheless problems have been encountered with regard to the technique and interpretation of echocardiograms in patients with suspected pericardial effusion Careful attention to the technique especially with regard to proper position of the transducer and angulation of the beam is essential If the transducer is angulated too medially the mitral annulus may be mistaken for the posterior wall and the echo free left atrial space behind it may be mistaken for pericardial fluid A large left pleural effusion may be confused with pericardial effusion In pleural effusions the sonolucent clear space behind the heart may vary with respiration In pericardial effusions there is no respiratory variation Placing the patients in the left lateral decubitus position to drain the pleural effusion may change the size of the sonolucent space posteriorly whereas in pericardial effusion this maneuver has little effect Soulen and associates have proposed placing the transducer over the left side of the chest in the posterior axillary line and recording a sonolucent clear space between chest wall and lung tissue thus establishing the diagnosis of pleural effusion It has also been suggested that a large sonolucent space posteriorly without an anterior effusion is more likely to be a pleural effusion However loculated posterior pericardial effusions without anterior effusions have been reported in patients undergoing open heart surgery Several investigators have proposed that with M mode scanning pericardial effusions can be clearly differentiated from pleural effusions Generally pericardial fluid is seen to appear at the atrioventricular junction and increases as the beam scans from base to apex In pleural effusions a symmetrical or equal sonolucent zone is observed behind the left atrium and left ventricular posterior wall Virtually no fluid accumulates behind the left atrium since it has been widely regarded that there is no potential space behind the left atrium However in a recent study by Lemire and associates pericardial fluid has been demonstrated behind the left atrium In addition pericardial reflection behind the left atrium attaching to the pulmonary veins has also been demonstrated Thus what was once regarded as a specific and reliable sign of differentiating pericardial effusion from pleural effusion has not stood the test of time

False positive echo free spaces posteriorly have been reported in the patients with pulmonary infiltrates and in the presence of a giant left atrium False positive echo free spaces anteriorly have been described in the presence of adipose tissue (epicardial fat pad) connective tissue or lung separating the anterior wall of the right ventricle from the chest wall Epicardial cysts dermoid cyst and lipomas or liposarcoma could cause large sonolucent anterior spaces Another cause of false positive anterior sonolucent space has been reported in patients with herniation of the stomach through the foramen of Morgagni

The quantitation of pericardial fluid by echocardiography has aroused a great interest among investigators Experimentally in dogs a minimum of 50 ml of pericardial fluid is necessary before the echocardiogram reliably demonstrates an effusion In a recent study by Horowitz and colleagues patients with suspected pericardial effusion by echocardiography underwent cardiac surgery More than 15 ml of pericardial fluid was found when a posterior echo free space persisted throughout the cardiac cycle between a flat pericardium relative to the epicardium The presence of combined anterior and posterior echo free space especially with a flat pericardium was indicative of a moderately large pericardial effusion On occasion anterior echo free sonolucent and/or posterior echo free sonolucent spaces with a relative stationary pericardium may be found in the absence of pericardial

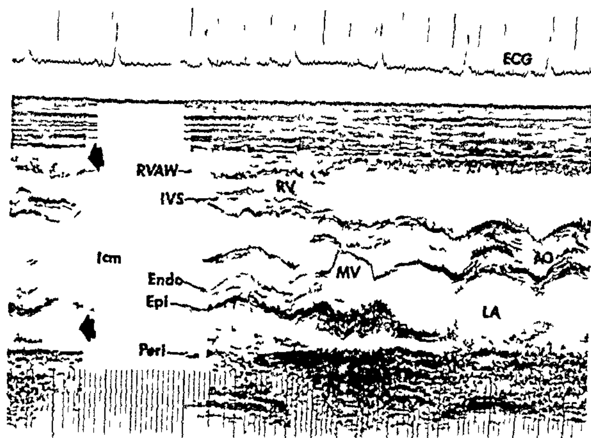


Fig 13 Definite echo free spaces anteriorly and posteriorly (*thick arrows*) in a patient with thickened pericardium and no fluid at surgery Abbreviations *RV* = right ventricle *RVAW* = right ventricular anterior wall *IVS* = interventricular septum *Endo* = endocardium *Epi* = epicardium *Peri* = pericardium *MV* = mitral valve *AO* = aorta *LA* = left atrium

effusion We have observed echo free spaces anteriorly and posteriorly in three patients with thickened pericardium (Fig 13) demonstrated at surgery With large effusions a swinging motion of the heart may be recorded[117] Exaggerated motions of the walls of the heart, septum, and mitral valve have been described[12] Pseudo prolapse of the mitral valve has been demonstrated in patients with massive pericardial effusion[139]

Coronary artery disease

The most significant application of echocardiography would be in the evaluation of patients with coronary artery disease However it is not uncommon for the patient with significant three vessel involvement to have a normal echocardiographic study The indirect consequences of coronary artery disease, such as left ventricular enlargement or segmental areas of abnormal wall motion can be demonstrated by echocardiography Posterior wall excursion and mean posterior wall velocities have been reported to be reduced in patients with myocardial infarction[111] In addition, abnormal systolic and diastolic bulges have been described[131] These findings are unreliable and not useful in the over all evaluation of patients with coronary artery disease

Ventricular aneurysms can rarely be defined by standard one dimensional M mode echocardiographic scanning However when the normal tapering effect is not observed during scanning from the base to the apex of the heart, an apical aneurysm should be suspected Anterior wall aneurysms may be totally missed by echocardiography because the ultrasound beam traverses the septum and posterior left heart wall only

Patients with end stage coronary artery disease and severe congestive heart failure may be echocardiographically indistinguishable from patients with congestive cardiomyopathy Both patients with severe coronary artery disease and congestive cardiomyopathies have dilated left ventricles Although Corya and associates[13] demonstrated that the sum of the amplitudes of motion of the septum and posterior wall endocardium was helpful in differentiating the two groups some overlap between the groups did occur Thus in cardiomyopathy the mean sum of amplitude of motion of the left side of the septum and posterior wall was 1 0 cm while in coronary artery disease

it measured 1 71 cm Nevertheless for the individual patient this type of measurement may be meaningless and may result in an erroneous diagnosis

The use of echocardiography in acute myocardial infarction has been reported [133] Two findings that were useful predictors of mortality were an enlarged left ventricular internal dimension and an abnormal mitral valve closure [133] Echocardiography may yield false information with regard to left ventricular function in patients with left ventricular asynergy The technique should not be regarded as the method whereby precise information can be obtained in patients with acute myocardial infarction

Bacterial endocarditis

The echocardiographic manifestations of valvular vegetations are characterized by an apparent thickening of the valve with normal motion of the leaflets unless the valve leaflets are involved by previous rheumatic or degenerative processes In addition the thickening has a shaggy appearance and may be non uniform [3] Mitral valvular vegetations have to be distinguished from mitral stenosis with a fibrosed or calcified mitral valve prolapse with redundant leaflets and atrial myxoma In mitral stenosis the dense echoes are uniform and not shaggy and the valve motion is abnormal In atrial myxoma the dense band of echoes behind the mitral valve can be traced toward the left atrium whereas valvular vegetations are attached to the valve and do not extend into the left atrium unless there is an associated flail leaflet On occasion left ventricular volume overload and flail mitral valve leaflet may be detected [3]

Several recent reports[138] have described a varying pattern of motion and appearance of the aortic valve in patients with aortic valve endocarditis Irregular or shaggy thickening of the right or noncoronary aortic leaflets is highly suggestive of aortic vegetations

The echocardiographic features in aortic bacterial endocarditis have to be differentiated from calcific aortic stenosis and a bicuspid aortic valve Calcification of the aortic valve usually produces more dense echoes which persist throughout the cardiac cycle Congenital non calcific aortic stenosis may also produce multiple linear diastolic echoes and the aortic valves may close in an eccentric position The systolic and diastolic appearance of the aortic leaflets in endocarditis may vary greatly depending on the angle of the transducer [138] In addition artifacts may be produced in normal valves because of improper gain setting or because of an unfocused or too intense printing light [139] Nevertheless while echocardiography may be useful in the diagnosis of bacterial endocarditis and valuable in assessing the hemodynamic consequences of acute aortic insufficiency, normal echocardiograms may be recorded in patients with bacterial endocarditis Vegetations less than 2 to 5 mm in size may be completely missed by echocardiography

Echocardiography has allowed recognition of unsuspected pre existing heart disease Serial echocardiography is helpful in the early detection of a changing pattern but each laboratory must develop its own criteria for interpretation based upon the equipment and quality of the recordings Unfortunately echocardiography does not differentiate between active and healed lesions

Atrial septal defect

The characteristic echocardiographic features of atrial septal defects with large left to right shunts are the increased right ventricular internal dimension and an abnormal pattern of ventricular septal motion These echocardiographic findings are indistinguishable from right ventricular volume overload of any cause Under rare circumstances the classical echocardiographic features may be absent in such patients if there is

1 a small left to-right shunt (pulmonic to systemic flow ratio $Qp/Qs < 1.2$ to 1.3),[141, 142]

2 pulmonary hypertension [3, 5]

3 associated shunt at the ventricular level [3, 5]

4 associated left ventricular volume overload [3] and/or

5 pulmonary stenosis [142, 143, 144]

Endocardial cushion defect

Endocardial cushion defect is a generic term that includes a spectrum of cardiac lesions characterized by an underdevelopment of both the anterior and posterior endocardial cushion in the atrioventricular canal with resultant deformities and/or defects of the atrioventricular valves and the intracardiac septa The ostium primum defect generally consists of small mitral cleft and a low atrial septal defect Complete endocardial cushion defect consists of atrial and ventricular septal

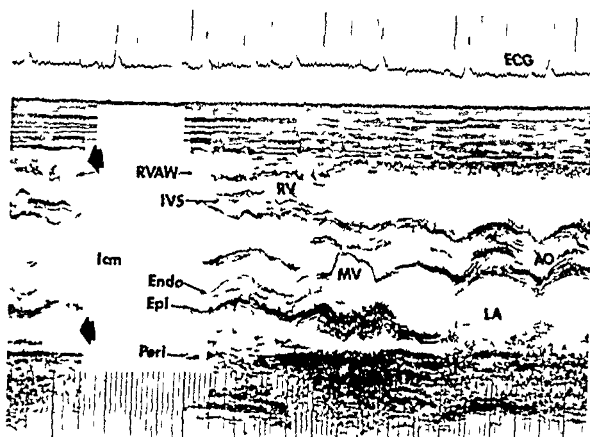


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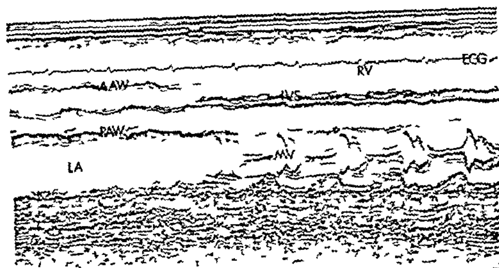


Fig 15 Echogram demonstrating that with rapid transducer angulation during M mode scanning from aortic area to base of ventricle there is pseudo overriding of the aorta with the aorta straddling the interventricular septum In addition the mitral valve is displaced posteriorly in relation to the posterior aortic wall Abbreviations *AAW* = anterior aortic wall *PAW* = posterior aortic wall *IVS* = interventricular septum *RV* = right ventricle

tation of echocardiograms Other technical problems may include

1 lateral resolution—the ability to distinguish clearly lying structures in a line perpendicular to the axis of the sound beam

2 drop out phenomenon—the sudden loss of echoes from an anatomic structure in the ultrasonic beam

3 spurious echoes [4]—echoes that do not relate directly to the specific cardiac structure and

4 reverberations—false echo impression of a second interface twice as far from the transducer as the first interface

These potential problems in technique must be taken into account in every examination Echograms may demonstrate an abundance of echoes This may occur as a result of problems of lateral resolution as well as with problems of gain setting When the gain setting is too high overlapping echoes are recorded making identification and location of each specific interface or structure difficult By contrast if the gain setting is too low vital information may be missed

Summary

Newer diagnostic applications as well as the ability of obtaining physiologic information has resulted in a greater interest in echocardiography As with any new technique certain classical criteria have not been found to be as specific and diagnostic as was originally believed This review has focused on the more important clinical applications in echocardiography We have not attempted to discuss every single clinical entity A critical evaluation as to the sensitivity and specificity of echocardiography in each clinical application is necessary A thorough knowledge of the basic principles of ultrasound a familiarity with recording devices and a realization of the pitfalls and limitations of the technique in each cardiac disorder is essential Hazards of echocardiographic interpretation may actually hamper its development as a diagnostic tool Before embarking on complex and sophisticated two dimensional echocardiography problems with regard to technique and interpretation of M mode echocardiography must be overcome

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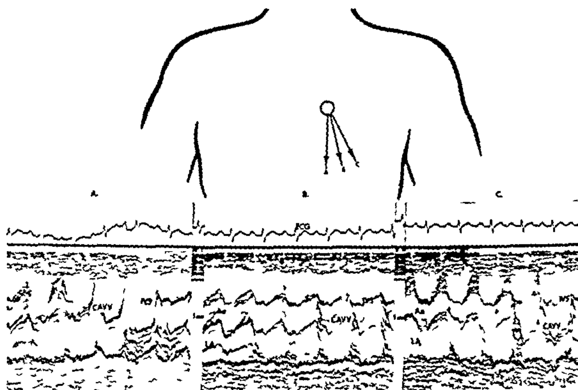


Fig 14 Upper diagram demonstrates the varying transducer positions marked *A* *B* and *C* on the chest as the transducer is angulated off the aortic root to obtain the atrioventricular valve in a patient with a complete endocardial cushion defect *Lower panel A* shows the common atrioventricular valve traversing the interventricular septum and appears to arise anteriorly almost at the same plane as the aortic leaflet *Panel B* shows that the common atrioventricular valve arises from the posterior aortic wall and also appears to traverse the septum moving anteriorly into the right ventricle *Panel C* shows that with lateral angulation of the transducer the leaflet now has no motion through the interventricular septum and has a large amplitude of motion within the left ventricular cavity

defects and a single primitive atrioventricular valve Incomplete or partial cushion defect is an intermediate group with defects in the mitral and tricuspid valves Thus a variable echocardiogram would be obtained, depending on the underlying disorder

The transition between partial and complete A V canal may not be as simple as previous investigators have implied[11, 11] Various echocardiographic patterns may be obtained in the same patient depending upon the spatial orientation of the beam in relation to the mitral tricuspid valve or the common atrioventricular valve (Fig 14)

Tetralogy of Fallot

Numerous reports have attested to the reliability of the echocardiographic diagnosis of tetralogy of Fallot[14, 1] Morris and associates reported on the largest series of patients with tetralogy of Fallot The most characteristic echocardiographic feature in their series of 25 patients was aortic overriding[15] Additional echocardiographic findings include aortic root enlargement an anteriorly situated aorta right ventricular enlargement decreased right ventricular outflow tract and abnormally thickened interventricular septum[1]

Technique is important in assessing these abnormalities Transducer position can produce variations in the right ventricular outflow tract Rapid angulation of the transducer, from a cephalad and medial position to an inferior and lateral position during M mode scanning of the aortic mitral valve axis can produce pseudo overriding and apparent displacement of the mitral valve in relation to the posterior aortic wall (Fig 15) In addition posterior displacement of the mitral valve in relation to the posterior aortic wall (usually 1 0 cm or greater) previously regarded as a sign of double outlet right ventricle [1] has been reported in patients with tetralogy of Fallot[1] truncus arteriosus[1] and in patients with an enlarged left ventricle[1]

Technical problems

This review has dealt with problems in transducer placement, beam angulation and interpre

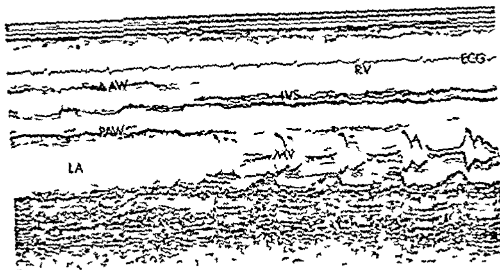


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Appraisal and reappraisal of cardiac therapy

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Cardiac pacing and pacemakers V Technical aspects of implantation and equipment

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Cardiac pacemaker implantation has been by two routes which have waxed and waned in relative popularity since the first brief transthoracic implant of a rechargeable pacemaker in 1958[1] The earliest pacemakers were designed to be implanted by anterolateral mid sternotomy or posterolateral thoracotomy[2,3] With demonstration that transvenous electrodes in use since 1959 could be left in place indefinitely with continued stimulation and that infection and dislocation of transcutaneous electrodes placed by thoracotomy or transvenously could occur the first pulse generators and electrodes for total transvenous implant were made available in 1965 Despite the success of thoracotomy implant the average age at implant 70 to 72 years (25 per cent of all patients are 80 to 90 years of age) discouraged the widespread use of thoracotomy and general anesthesia Transvenous implant became dominant rapidly and has remained so as local anesthesia causes only a slight physiologic disturbance during implant That route is suitable for patients of any age or disability

Transvenous implantation

With local anesthesia and light sedation the cephalic vein is sought in the delto pectoral groove via an overlying incision[4] The electrode is introduced readily into the apex of the right ventricle and insinuated beneath a trabeculum[5] Satisfactory *position* should be ascertained in posteroanterior *and* lateral fluoroscopic projections as the right ventricular apex is displaced in the diseased enlarged and rotated heart Right ventricular angiography may be helpful *Threshold* of stimulation amplitude, and slew rate or frequency of the endocardial *electrogram* should all be ascertained (see Cardiac pacing and pacemakers section III)[6] If all are satisfactory, the lead is fastened to the cephalic vein with 3 to 4 ligatures of synthetic non absorbable material size 0 or 00 Finer material may cut the electrode insulation and silk though non absorbable will loosen with time allowing the electrode to be pulled from the heart[7] A satisfactory alternative is the use of a silicone rubber butterfly' sutured to the surrounding tissue and attached to the lead by silicone rubber cement[8] If the cephalic vein is not suitable either the external jugular or internal jugular vein may be used The external jugular vein is no more frequently available than the cephalic, but either may be found when the other is absent As a last resort, the internal jugular may be entered by lateral venotomy and a purse string suture placed about the point of entry of the lead or the vein may be ligated In either event no difficulty need be anticipated[9]

The lead is then tunnelled to a subcutaneous position inferior and medial to the delto pectoral incision and attached to the pulse generator It is most important that the pulse generator site be of adequate size so that the skin is not tight and that careful hemostasis and sterility be practiced as the pacer site may fill with blood should a vessel remain unsecured Infection is almost untreatable by any method other than removal of all the pacer hardware and later replacement at another site[10,11] The pacer may be wrapped in a polyester sac to assist fixation to the pectoral fascia It should not be sutured to the fascia through the hole in the generator provided for this purpose as the non absorbable suture may become a fulcrum

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Table I Patient data using the Biotronik IVE 185 transvenous electrode

Patient	Rhythm	No of previous procedures	Associated disease	Implant data			
				Electrogram	Threshold ma at 1 msec	Date	Result
MC	AF with CHB	0	Mitral insuff	5 mv 1 1 v /sec	0 3	5-20-76	Spurious signal
						5-24 76	Revision OK
AM	AF with CHB	2	Adult ASD	5 mv 1 4 v /sec	1 0	9-2 76	OK
SH	LBBB	4	ASHD large RV	8 mv 7 v /sec	0 5	12 1 76	OK
HS	AF with CHB	0	ASHD large RV	17 mv 6 v /sec	0 4	1-4 77	OK
GH	CHB	3	Ebstein's anom	6 mv 1 ? v /sec	0 75	10-14 76	OK
MW	SSS	2	CHF large RV	8 mv 4 v /sec	0 4	8-27 76	OK
PG	SSS	0	CHF large RV	19 mv 8 v /sec	0 6	7 1 76	OK
AP	CHB	5	Myocardiopathy	11 mv 4 v /sec	0 9	6-2? 76	OK

about which the electrode may be caught and disrupted Wound closure is best in two layers with a continuous subcuticular layer of 000 Dexon which need not be removed

Transvenous electrodes

There are two varieties of transvenous electrodes those which attach *passively* or *actively*' to the endocardial surface Both may be unipolar or bipolar Progressively smaller tip electrodes have become available recently introduced electrodes are 8 to 10 mm in surface area though larger less efficient electrodes remain available The prolonged longevity claimed for many of the newer pulse generators is predicated on the restricted output required for the newer more efficient electrodes (see Cardiac pacing and pacemakers section IV)

One of the major indications for transthoracic implantation has been the occasional inability to hold a transvenous electrode in the apex of the dilated hypertensive smooth walled right ventricle The reported displacement rate for the passive transvenous electrode is between 1 5 and 21 per cent Electrodes have been designed which *actively* grasp the endocardial surface Three are commercially available one has four nylon barbs which diverge from the stimulating surface and are ejected to grasp the endocardium or retracted to remove the electrode another has fine metal wires held on a piston within a cylinder at the electrode tip † Once the appropriate position is found the wires are forced from the electrode tip The third has four silicone rubber tynes projecting from the tip‡ which can provide additional fixation At least two other electrodes for fixation in the ventricular apex are in clinical evaluation One is a modification of the myocardial sutureless or screw in electrode [1] § the other has a balloon at the tip to be inflated when insinuated beneath a trabeculum (which may not be possible in the hypertensive ventricle) [4] || Adequate data is not available for a full assessment of the last three electrodes (Table I)

Myocardial implantation

The transthoracic route was used *exclusively* for fully implanted pacemakers until 1965 when effective transvenous equipment was introduced [26] Interest in thoracotomy persisted as an alternative when the transvenous route was unsuccessful or for any reason impossible [22]

Dexon manufactured by Davis & Geck Pearl River N Y

*Vitatron MIP2000, Vitatron Inc Boston Mass.
†Biotronik IVE18 Biotronik Sales, Inc St Petersburg Fla
‡Medtronic No 6951 Medtronic Inc., Minneapolis Minn.
§Medtronic No 6954 Medtronic Inc Minneapolis Minn
||Siemens-Elema No 289 Siemens-Elema Elk Grove Ill

Table II Right ventricular implants

Patient	Rhythm	Route	Electrode	Defect	Revision data: Electrogram	Revision data: Threshold ma at 1 msec	Resolution	Date	Result
S F	ICHB	OHS	Cordis Epi	NS/NP	—	10 4	Transvenous implant	12 27 7?	Ok
J B	CHB	OHS	Cordis Epi	NS	9 mv 0 8 v/sec	1 6	Hi sensitivity pacer	4 25 73	Ok
G K	ICHB	Subxiphoid	Medtronic 6917†	NS & ventric tachycar	0 8 mv 0 3 v/sec	4 9	Transvenous implant	4 17 75	Ok
M H	LBBB	OHS	Medtronic 6913	NS	11 mv 0 7 v/sec	1 3	Hi sensitivity pacer	7 18 75	Ok
E R	CHB	L subcostal	Medtronic 6917†	Diaphragm twitch for 31 mos	15 mv 2 2 v/sec	3 8	Unipolarize	10 23 75	Ok
S S	BBBB	L anterolateral thoracot	Medtronic 6917†	NS	5 mv 0 3 v/sec	1 2	Reimplant in left vent	11 18-75	Ok
A R	CHB	L subcostal	Medtronic 6913†	NP	6 mv 0 5 v/sec	13 2	Transvenous implant	6-22 76	Ok
J I	CHB	L anterolateral thoracot	Medtronic 6913† and 6917†	NP	8 6 mv 0 7 v/sec	12 3	Unipolarize to 3 5 ma electrode	8 2 76	Ok
T L	ICHB	Subxiphoid	Medtronic 6917†	NP	11 mv 1 2 v/sec	8 4	Unipolarize higher output pacer	10 16 76	Ok
M M	SSS	Subxiphoid	Medtronic 6917†	NS	2 mv 0 8 v/sec	3 2	Hi sensitivity pacer	12 30-76	Ok
D Z	2 1 HB	OHS	Medtronic 6913	NP/NS	5 mv 0 4 v/sec	11 3	Transvenous implant	1 11 7	Ok

Abbreviations ICHB = intermittent complete heart block NS = not sensing NP = not pacing OHS = at open heart surgery via median sternotomy
†At another institution

Mortality may be higher via thoracotomy[3] than transvenously but with careful management the mortality rate for thoracotomy should be quite low As always results are based on careful patient selection and on the experience and skill of the operator

One transthoracic route which has been used infrequently was through the mediastinum avoiding the pleural space While it was possible to use older transthoracic electrodes via a limited mediastinal exposure these were far more easily sutured to the heart with adequate transpleural exposure The first new myocardial electrode in many years was sutureless corkscrew in shape held at the end of a 20 cm long introducer for placement into the left ventricle It can be placed via a limited incision remote from the heart i e left subcostal or subxiphoid thoracotomy and has reawakened interest in the surgical approach Some implanting surgeons have always felt more comfortable in the operating than the fluoroscopy suite and far more confident of sterility in the former so that approximately 15 to 20 per cent of all pacer implants now employ sutureless electrodes

The two problems of the sutureless electrode exist because of the most widely used surgical approach

1 The left ventricle is a far better site for pacing than the right because of the thickness of the left ventricular wall and the amplitude of the electrogram which can be obtained The right ventricular myocardium is thin the electrode penetrates 6 mm and the stimulating tip may be within the right ventricular cavity and not within the muscle[2] This has been enough of a problem to have prompted the introduction of an electrode of 4 mm penetration the results of which have not been evaluated The electrogram which triggers the non competitive pacemaker is largely left ventricular in origin and the further the electrode(s) is from left ventricular myocardium the more likely it is that the signal will be inadequate to trigger the generator (Table II) The transvenous implant is successful because the apex of the right ventricle is formed by right ventricle and

ventricular septum which is of course left ventricle

During implant by the limited subcostal thoracotomy only an *anterior* approach to the heart is possible In the normal heart a rim of left ventricle is readily available for electrode implant If the right heart is enlarged or dilated or if the heart is rotated the left ventricle will be posterior and still less approachable There are three routes used for the sutureless electrode implant One is an upper abdominal midline incision with the resection of the xiphoid through which only the diaphragmatic surface of the heart can be approached[8] The authors have been referred seven pairs of sutureless electrodes implanted into diaphragmatic surface of the right ventricle which failed early after implant with either loss of sensing or pacing or both

The second right ventricular exposure is via a transxiphisternal incision also with resection of the xiphoid With careful measurement of sensing and pacing functions with a probing electrode this route had been considered promising but has also been abandoned in favor of a left ventricular approach Third the left subcostal incision allows posterior left ventricular exposure and is to be preferred

A new approach by the developers of the transxiphisternal route is directly to the left ventricle by a left anterior axillary line incision in the fifth interspace This patient lies recumbent on the operating table elevated to the level of the operator s chest A short (8 to 10 cm) incision allows entry into the left pleural space and exposure of the largely posterior left ventricle The electrode is placed with the introducer through the opened pericardium General endotracheal anesthesia is required Twenty cases have been implanted without difficulty

2 Laceration of the thin remote right ventricle (or left ventricular apex) can occur Full thoracotomy will be required urgently to avoid exsanguination Several patients are rumored to have died of this complication though only a single case report of exsanguination exists

Thoracotomy implant may be used

1 Whenever the chest is already open i e during thoracotomy for cardiopulmonary bypass remembering that during median sternotomy the right ventricle presents and the heart should be elevated to approach the left ventricle

2 If no fluoroscopic capability exists or if no one skilled in transvenous electrode technique is available

3 For the rare failure of transvenous pacing

4 For some instances of atrial synchronous pacing

5 For many (but not all) childhood pacer implants[11] If thoracotomy implant is performed the left ventricle is preferred

Programmable pacemakers

One of the most significant recent developments certain to assume even greater future importance is that of non invasive programmability of pulse generator parameters [1] Minimal or non invasive variation of pacemaker function is not new The earliest generators allowed percutaneous needle operation of a potentiometer to vary output and rate and the operative short circuit of a resistor to increase output Other units had two rates usually 70 and 85 to 90 with a bistable magnetic switch leaving the rate at the low or high setting Both techniques were of limited interest because it was not then appreciated that reduction of output would increase pulse generator longevity and it eventually became clear that in the presence of complete heart block a rate of 90 added little to the patient s exercise tolerance compared to a rate of 70

Other variability such as the external addition of a temporary reverse current to the output circuit of a generator allowed the accurate assessment of threshold as a function of pulse generator output[3] This technique too has had limited use because of the recognition that stimulation threshold is stable chronically and that its infrequent change is a poor predictor of impending battery exhaustion

Another pulse generator is designed to reduce its output when a magnet is placed over it in 16 steps of 0 35 volts from full output of 5 4 volts to zero and at a rate of 100 per minute [5] The threshold of stimulation can be determined but sustained reduction of output cannot be accomplished As the pacer rate also falls with decline in battery voltage and as long term threshold is stable it seems to have little advantage especially as a demonstrated low stable threshold cannot allow fixation of a low output

In 1970 variation of pulse duration with a fixed output voltage by a magnetically activated potentiometer allowed both threshold determination and fixed reduction or increase in pacer

output Reduction of impulse duration is accomplished mechanically and non invasively by the transcutaneous magnetic rotation of two bar magnets attached to a gear operated variable condenser The variation in pulse duration reduces charge output per impulse at shorter impulse durations Rate is fixed [41]

Using the option of output reduction, it is possible to pace patients chronically at one half or less of the battery drain of the factory delivered output With chronic pulse duration reduction to 0 25 to 0 30 msec the longevity of this generator has been prolonged with a cumulative survival rate of 96 6 ± 2 4 per cent, 42 to 45 months after implantation [4]

The most ambitious attempt at programming was introduced in 1972[43] and allowed the non invasive programmability of both rate and output with impulse duration variation as a function of rate Six rates 60 65 70 80 90, and 100 per minute and in another model 50 60 65, 70 100, and 120 are available The pulse duration is 1/512 of the *period* between impulses (the reciprocal of the pulse generator rate) [44] Output can be adjusted over four steps which correspond to voltages of 4 5 *high* 3 0 *medium*, 2 0 *low*, and 1 15, *test* If the electrode impedance is 500 ohms the current outputs will be 9 6, 4 and 2 3 milliamperes respectively Setting both the output level and the pulse duration (by manipulation of rate) 24 levels of output can be selected to determine threshold and a level of output selected which drains the battery at a lower rate The early units of this model had moisture entrapped in the hermetically sealed circuitry and a high failure rate More recent models have been stable and reliable The cumulative survival rate has been 68 8 ± 10 2 per cent 42 to 45 months after implantation *

Rate variability has not been widely used as the bulk of patients are controlled well at 70 per minute and tachycardias are not usually more satisfactorily managed at rates above 80 per minute It may be that the slower rates 50 to 65 will be more valuable in the treatment of patients with

1 Inoperable coronary artery disease in conjunction with propranolol which reduces myocardial oxygen consumption and cardiac rate Excessive rate reduction can be controlled with a pacer but it is illogical to reduce myocardial metabolism and then increase the rate to 70 per minute A rate of 50 seems more suitable in some patients

2 Extreme sinus bradycardia in the elderly may be as low as 20 to 25[45] per minute though they may be asymptomatic at 50 per minute[46] and congestive failure may occur at 70 per minute A slower paced rate may resolve the problem of extreme bradycardia and avoid a rate that may be deleterious

Other units offer rate programmability with R F impulses over a range of steps of 30 60 to 100* or by operation of a magnetic switch with a range of 60 to 104 with successive steps of 6 BPM † Since rate variation offers little at this range these units add little to the capability of pacing

Of greater interest is the availability in the near future of programmability of pulse duration (without rate), output voltage sensitivity, refractory period and rate in the same unit Programming will aid sensing of the poor cardiac signal by increase of sensitivity and in reduction of electromagnetic interference by reduction of generator sensitivity The more distant future will see programmability, far removed from the present simple functions of parameters needed to terminate tachycardias ‡

Despite the availability of a broad range of programmable parameters the availability of a cheap simple pacemaker with a single rate and output will remain desirable Further problems may arise with the programmed functions Spontaneous and unwanted reprogramming with the pacer in the magnet mode[47] exists and reprogramming by electromagnetic interference may occur Reprogramming may cause serious problems if output is reprogrammed below threshold of ventricular capture As rate has become the universal indicator of power source depletion and may now be reprogrammed inadvertently or during a test at a facility not providing a patient s pacer follow up it is possible that pulse generator malfunction may be mistakenly assumed The

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†Prolith 21S Edwards Laboratories Santa Ana Calif

‡An atrioventricular sequential (DVI) programmable pulse generator capable of ventricular inhibited (VVI) pacing at 70 per minute or A V sequential (DVI) pacing at an A V delay of 125 150 or ?50 msec and over all rates of 63 71 9 and 109 is soon to be introduced Model 1 81 Medtronic Inc Minneapolis Minn

industry should begin to move toward the selection of indicators of power source depletion and malfunction which will remain independent of programmable parameters. These should be safe, detectable by conventional ECG, telephone transmittable, and recognizable on electronic analysis of pacer function. A possible indicator may be the adoption of a specific rate which will never be programmed, or a frequency transmitted by the generator and radio frequency detected such as the musical tone A (440 Hz).[48]

Unipolar vs. bipolar pacing

The terms unipolar and bipolar refer to the number and polarity of the electrodes in (or on) the heart. *Each electrode is really bipolar as* cathode (serving as source) and anode (sink) are required for current flow. Whether the electrode is termed unipolar or bipolar is determined by the location of the two output terminals relative to the portion of the heart being stimulated. The negative terminal (cathode) must be stimulating in all instances, while the anode may be stimulating or may be remote.

The electrical discharge which stimulates the heart through the cathode will reach the anode *equally well whether it is intracardiac or elsewhere* within the body and current thresholds of cardiac stimulation are equal for both unipolar and bipolar. Both have been in successful widespread use since the beginning of clinical cardiac pacing. Though more bipolar than unipolar electrodes have been implanted, more manufacturers have selected unipolar systems which are beginning to dominate the field. The relative merits of the two can indicate specific utility of one, such as unipolar for occasional enhanced sensing or bipolar for resistance to electromagnetic interference (see Cardiac Pacing and Pacemakers, section III).

Electrocardiographic detection of the unipolar stimulus is easier than the bipolar, for analysis of pacemaker function and for transtelephone transmission. Unipolar pulse generators are more sensitive to EMI, especially that produced by muscular movement. Bipolar electrodes are more resistant as both terminals are intracardiac and remote from skeletal muscle. Alternately, an occasional proximal intracardiac terminal of a bipolar system will be near the atrium *and falsely* sense and cycle from a P wave, virtually impossible for a unipolar pacer.

The relative safety of bipolar vs. unipolar pacing has been questioned because of the demonstration that all recorded episodes but one of pacer related ventricular fibrillation have been in the presence of bipolar rather than unipolar pacing.[30, 31]

Sensing of the ventricular electrogram acutely and chronically is virtually equal. Chronically the ventricular fibrillation threshold is equal because of loss of anodal sensitivity. The unipolar EMI sensitivity is greater. On balance there is probably little to choose between the two for implanted pacing.

Modes of pacing

Asynchronous (VOO) is the oldest pacing mode.[32] Stimulation is at a predetermined rate without modification by spontaneous cardiac rhythm and is useful only for complete heart block without interpolated premature ventricular contractions. Pulse generator longevity often has been greater than for triggered pulse generators but as longevity of all pulse generators is rising rapidly now, it is likely that its sole significant virtue (greater longevity) will vanish. Competition with spontaneous cardiac activity has been reemphasized by the premature ventricular contractions found in patients with complete heart block during exercise and daily activity, increasing the possibility of competitive ventricular fibrillation.[33] Asynchronous pacing remains useful and is not yet obsolete but may become so in the near future.

Non competitive pacing falls into two categories, one of which, ventricular inhibited pacing, is the dominant pacemaker mode, accounting for 90 per cent of all pacemakers implanted.

Ventricular inhibited. This mode (VVI)[33]* (also called demand or standby) is the most widely used and available from every manufacturer. Stimulation is interrupted by spontaneous cardiac activity; resumption of stimulation may be at the interval between two consecutive pacing stimuli or the interval may be longer (positive hysteresis) in which a slower rhythm than the paced rate is allowed to develop, or it may be shorter (negative hysteresis) in which premature ventricular activity may be prevented by short

*The three letter code designates the mode of pacemaker operation as suggested in the report of the Intersociety Commission on Heart Disease Resources.

ening the interval between successive QRS complexes[56] *Positive hysteresis has been widely* used though negative hysteresis has been used for therapy of tachyarrhythmias only Ventricular inhibited pulse generators may *have the same* refractory period for pacing and sensing or one for pacing and another for sensing A variety of operating features such as rate, programmability pulse duration and output current and voltage differ between units of the same basic operation

Ventricular triggered (VVT) non competitive pacing was derived from atrial synchronous pacing and was the first clinically successful non competitive pacemaker[57] The first ventricular inhibited units failed because of excessive sensitivity to electromagnetic inferference[58] and unreliable *construction A stimulus is emitted into* each QRS complex and distorts the normal QRS complex Its use has become more limited as the problems of the ventricular inhibited (VVI) mode were solved Battery drain is high and longevity short Two triggered units resolved this problem by reduction of stimulus duration in response to a spontaneous ventricular contraction to produce little current drain and lose ability to stimulate the heart[5] Ventricular synchronous units of conventional output are still useful if a patient is expected to encounter extremely severe electro magnetic interference as conventional ventricular triggered units cannot be inhibited under any circumstances[6]

The Omni Ectocor (VVT)* (a programmable ventricular synchronous pacer) can be inhibited and recycled by an interfering stimulus falling just after the first of two pacer refractory periods During the remainder of the generator refractory period R *waves or other stimuli are incapable of* triggering the generator During the generator sensitive period it has a conventional synchro nous response[61]

Atrial synchronous (VAT) pacing introduced in 1962, was the first pacing mode responsive to cardiac activity to reach extensive clinical use It is useful only for patients with complete heart block a normal stable and physiologically responsive atrial rate and rhythm During atrial *arrhythmia*, the cardiac rate became difficult to manage despite the existence of electronic blocking mechanisms, and recurrent or continuous atrial fibrillation or flutter requires replacement by an asynchronous (VOO) or ventricular inhibited (VVI) unit The non competitive mode treats the bulk of arrhythmias which require *cardiac pacing Though atrial synchronous* pacing can be non competitive with conducted beats if the P R interval is longer than the A V delay,[9] it is not non competitive with idioventricular activity It is best implanted by thoracotomy and is infrequently used except for young people with a good myocardium capable of benefiting from increase in cardiac rate and output with increased ventricular activity and the unusual patient with such poor cardiac function that atrial synchrony is required to maintain cardiac output

A V sequential pacing (DVI) was originally designed for patients with acute myocardial *infarction and sinus bradycardia to* bring the benefit of atrial contribution to cardiac output Both A V sequential and atrial synchronous pacing can accomplish that goal if the atrial rhythm is stable[63] A V sequential pacing is required if the atrial rate is too slow and A V conduction is compromised Atrium and ventricle are both paced with an electronic A V delay

If there is a spontaneous ventricular contraction the pacemaker is inhibited and recycled both *for the atrial and ventricular stimuli* The Bifocal* pacemaker is technically difficult to insert The atrial electrode must be far from the ventricular so that the atrial stimulus is not sensed to falsely inhibit the ventricular output The unit is beneficial where atrial contribution is needed at a fixed cardiac rate especially (as is atrial synchronous) if atrioventricular valvular insufficiency is exacerbated by the loss of the normal A V sequence[64]

For most of the patients the additional contribution of the atrium seems to make little difference at usual levels of activity For a few it is very valuable In some patients with re entry tachycardia, the ability to set the atrial rate and the P R interval (i e the pacemaker A V delay) may with or without drug therapy interrupt the reciprocating pathway *and control the arrhythmia*[65] In others atrial synchronous pacing may accomplish this effect[5] Though still investigational control of re entry tachycardia may prove to be far more valuable than addition of the atrial contribution

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Atrial pacing

Atrial pacing either alone or in conjunction with pacing of the ventricles has long been attempted Initial atrial electrodes were sensors for atrial synchronous pacing[2] but more recently both sensing and pacing have been needed For ventricular pacing one endocardial and several epicardial approaches are available A variety of atrial approaches have been attempted each inferior to any ventricular route for consistency and ease of application. Atrial pacing is still not in widespread use but is gaining slowly in popularity

The development of somewhat improved transvenous atrial electrodes has encouraged their use and requires the existence of a stimulatable atrium (without atrial fibrillation) and reasonable A V conduction (or the use of A V sequential pacing in the presence of impaired A V conduction) The major indications for atrial pacing are

1 Sinus bradycardia with or without sinus arrest and with or without supraventricular tachycardia i e the brady tachy syndrome

2 Suppression of ventricular irritability with a rapid supraventricular rhythm

3 A V synchrony to increase cardiac output and

4 Rapid atrial pacing to terminate supraventricular[a] and reentry tachycardia

Atrial electrodes

1 A flat open coil electrode designed for the thoracotomy approach to atrial synchronous pacing can be sutured to the atrial epicardium Though designed to sense the P wave it can be used to pace but requires full thoracotomy for its application

2 Conventional transvenous ventricular electrodes which can be placed in the coronary sinus to pace and/or sense atrial activity

3 An electrode which has a J curve in the silicone rubber insulation and is placed into the atrial appendage Older versions did not maintain position permanently and pacing and/or sensing were erratic[a] but newer versions are more promising

4 A barbed electrode inserted through the lumen of an introducer catheter placed via the internal jugular vein is placed in the atrial appendage the introducer removed the barbs spring open and grasp the adjacent atrial wall[73]

5 The atrial electrode may be introduced by a modified transseptal needle from the saphenofemoral system to penetrate and grasp the atrial septum[a] The generator is placed in the lower abdomen from which the electrode descends to the femoral triangle in the thigh enters the venous system and ascends to the heart The approach has been used in one patient for atrial pacing[73] Were ventricular pacing also required that electrode would have to ascend from the abdominal pacer to the venous system at the neck

6 The most successful approach to transvenous atrial pacing has been that of placement of a special lead in the coronary sinus[74] Electrodes placed in the coronary sinus have been characterized by long term stability of threshold and generally satisfactory sensing of the P wave so that atrial inhibited or[77] triggered atrial pacing (AAI or AAT) or atrial synchronous pacing (VAT) can be performed

The initial electrodes placed in the coronary sinus were unmodified ventricular leads More recently a lead has been developed which has the sensing and stimulating ring 5 cm proximal to the tip The leading silicone rubber portion wedges in the distal coronary sinus to hold the electrode in position In limited evaluation this electrode has provided satisfactory long term pacing and sensing

The discussion above has described modes of implantation and some of the technical aspects of atrial and ventricular implant via the transvenous and transthoracic routes Both approaches are useful and each has specific areas of superiority For prolonged pacing more free of complexity the ventricular rather than the atrial route is *preferable* For either route programmable pacers offer rate and output variability to accommodate to a high threshold or increase longevity in the presence of a low threshold.

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Safety threshold of ultrasound in medical use?

Because of increasing medical use of ultrasound especially in diagnosis it has become important to check the threshold of their biological and more particularly of their genetic effects Most studies of effects of ultrasound on chromosomes applied at medical doses have shown no damage Nevertheless the absence of visible chromosomal damage does not at all exclude the possibility of damage to the DNA molecules This is most important as damage to genetic material (DNA) can lead to somatic mutations which are not only dangerous for the growing fetus but also might contribute to other disorders such as cancer etiology

As a first step in the elucidation of this question we searched for possible injuries of purified calf thymus DNA in solution caused by ultrasound on frequency and intensity typical of medical treatment both therapeutic and diagnostic

The ultrasound equipment we used was set at continuous waves Sonostat 633 Siemens for intensities down to 200 mW / cm (frequency of 2 MHz) and Sonicaid fetal heart monitoring for an intensity of 20 mW /cm (frequency 0 87 MHz) The DNA molecules were photographed on an electronic microscope the enlargement used was 29 000 and the lengths of sonicated and control molecules of DNA were compared

We found considerable damage for intensities commonly used for therapy i e 1 5 W /cm and 1 W /cm as well as for intensities as low as 200 mW /cm For all periods of duration tested (10 minutes to 120 minutes) all the DNA molecules were broken down These results are reported in detail elsewhere

For doses commonly used in diagnosis i e 20 mW /cm 1 MHz we found no effect But it is important to notice that an intensity of 200 mW /cm for which there was a drastic effect is only 10 times the intensity used for diagnosis and that these intensities are sometimes applied for periods of time which are much longer than those of our experiments for example for several hours in fetal heart monitoring during labor In addition it is known that sonication can pass through short peaks of much higher intensities than those given by calibration of the machine Furthermore as pointed out by Hill and by Jehensen and Breddel the specifications given for the ultrasound instruments are not necessarily exact For example a control calibration of the Sonostat apparatus we used gave 20 per cent higher intensities than those indicated Moreover not all manufacturers provide data on output intensity with their apparatus It is thus of highest importance to control the quality of medical ultrasound equipment

One must of course be aware of the fact that the above mentioned experiments were performed on DNA molecules in solution Under these conditions cavitation is the factor generally proposed to explain mechanical and chemical effects of ultrasound Hill however has pointed out that the cavitation which happens in the liquid state probably does not occur in organized tissues Therefore we have tried to work at conditions—frequencies of 2 MHz and 0 87 MHz volume of ml ambient pressure 1 bar temperature below 35 C—which were shown by Iernetti to be below the cavitation threshold The mechanism involved in the DNA breaks we have observed is thus not clear It could well be as Hill has suggested that ultrasound produces biological responses directly In this mechanism it is postulated that the repeated vibrations transmitted to the long thin DNA molecules produce shearing and that this mechanism might occur in vivo where cavitation is supposed not to happen

Thacker in a letter to *The Lancet* criticized our conclusions, arguing that were shear forces sufficient to disrupt DNA in chromosomes it is likely that damage to other cellular structures will be extensive enough to cause cell disruption and death We doubt however whether cell disruption and death will nessarily happen before DNA shearing Indeed DNA being the longest molecule in living cells is the most sensitive to shearing Moreover it is known that chromosome breaks happen at higher ultrasound intensities i e in the W /cm range thus the DNA is sheared yet the cells are not dead Furthermore the presence of chromosome breaks rather than chromatid breaks means that the cells were sonicated at G stage and later went on to cell division

Although our results cannot lead to a conclusion as far as their in vivo implications are concerned since the DNA is protected in the chromatin and in the cell structure it is nevertheless to be borne in mind that intensities which are only one order of magnitude higher than those used in diagnosis and which are lower than those used in therapy cause large scale fragmentation of DNA in solution Since these doses are uncomfortably close to those used in medical practice we believe that as long as we remain ignorant of their possible in vivo effect on DNA appropriate care should be taken when using ultrasound Uncontrolled peaks of high intensity should be avoided and exact calibrations of instruments must be performed

A study of ultrasound induced single strand breaks in DNA by a completely in vivo system is now in preparation In those experiments mice with cancerous ascite cells are sonicated and after cell lysis the DNA is fractioned on an alkaline saccharose gradient

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Society and the doctor

Between Western society and the medical profession there has developed a crisis It is part of a wider disenchantment with the effects of science and technology which it brings into focus because the issues seem personal fairly well defined and obviously ethical In Britain the effect of this crisis is seen predominantly in a gross divergence between the medical profession and the political left wing In America I suppose it underlines the malpractice insurance problem

Grave strains and difficulties were inevitable as medical practice changed rapidly in a society of prodigious change Yet elements of avoidable human failure and folly bear a large share of the blame In Britain I feel the government and the profession stand equally condemned For our own sakes and our patients sake it is imperative for us now to begin to repair the breach The essential part of that repair is to recover reasonable understanding and trust without which medical care will deteriorate catastrophically

Curiously a large element in the current distrust stems from attempts to enhance our prestige as a profession It has seemed obvious that publication of medical achievements would enhance public respect for the competence of doctors Because of the limitations inherent in medical practice however it was inevitable that a reaction would follow In part that reaction takes the form of a readiness to believe that medical failure is commonly due to negligence The attempt to defend ourselves against charges of negligence brings with it enormous cost because special investigations and potent medical treatment are intrinsically expensive Their expense is soaring as medicine advances and moreover can never make our work entirely reliable The emphasis which has been unwisely placed on science in medicine has further diverted the physician from a reliance upon his personal powers of assessment and interpretation (clinical acumen) to reliance upon special methods Where these investigations are ineffectual he tends to overlook possibilities In the critical area of human relationships the scientific approach has impaired his competence (Only this week I heard of a woman who suffered a period of agonizing fear because a Gynecological Registrar bluntly and without qualification or encouragement told her that a lump had been found The lump could well prove simply to be inflammatory)

The very foundation of medical practice was is and will remain trust between patients and doctors This trust is not dependent upon omniscience or omnipotence It grows more easily between people who humanly recognize their own needs and limitations The best start for a doctor is not science and technology It is awareness of his own humanity Medicine is not for them it is for us

A man I know recently had a very severe attack of chest pains Excellent physicians diagnosed a myocardial infarct but proof was lacking Talking about him with cardiologists I gather that with the aid of E C G enzyme assessments and coronary angiography virtual certainty of diagnosis can be achieved in well over 90 per cent of cases The attending physician must however feel free in order to judge best whether say coronary angiography is justifiable in such circumstances Again the best interest of the patient is served if his physician judges freely whether or not to recommend major and costly changes of life style The most frequent duress upon a physician s judgement is the need to appear to have neglected nothing if disaster supervenes If in such a case he advises major restrictions upon the patient s life the physician is protected but the patient may be greatly impoverished. The loss would be especially tragic if the pain is merely referred from such a benign lesion as an acute dorsal disc lesion This diagnosis could I believe often be made only by exclusion

Resources are very limited Enormous expenditure upon medical service is simply not an economic way to produce the good life If we use resources to defend ourselves against the appearance of negligence something else must be forfeited (In Britain most of our permanent renal failure patients die because we cannot afford to dialyse them and we funked the moral problems of transplantation)

Who can best decide for each patient when the sensible limits of expenditure have been reached? Only his physician can do this taking into account all relevant factors If he is to accept this responsibility the physician must know that his judgement is greatly protected and will be upheld even if misfortune follows Such a trust really makes us judges in our own cause though it is necessary for the well being of all To be worthy of this trust is a man size challenge indeed Its

recovery however should enable us confidently to use advances in medicine for blessings whereas now sometimes they appear to be millstones round our necks In order to recreate that trust we need deeper and wider thinking about our work than generally we have shown We need candor and simple good will Above all we need to prove that science in medicine is but the handmaid of compassion that personal fortune and the esteem of our peers is entirely secondary to the trust and care that must lie between man and man.

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Engl. 3

Of pre-infarct syndrome and bed rest

The emphasis in the management of ischemic heart disease and myocardial infarction is directed mainly toward the treatment of myocardial infarction and its many serious complications after the infarct and its complications develop *Mobile CCU hospital CCU medical management* and coronary bypass surgery command most attention and space in medical literature today concerning the management of myocardial infarction *Prevention* of infarction is not adequately emphasized The greatest advancements in all fields of medicine have been in the field of prevention It is well known that pre infarction angina is likely to lead to myocardial infarction therefore why not treat the pre infarction angina vigorously with the objective of preventing infarction rather than wait for the infarct to develop and then treat it? Treatment to prevent infarction should begin promptly after the first signs of pre infarction angina are manifested if infarction is to be prevented It is always better to treat ischemic heart disease before any heart muscle is lost in an attempt to prevent infarction with the loss of myocardium than to treat an infarct after heart muscle has been lost Heart muscle cannot regenerate and therefore an infarct of the myocardium represents an area of heart muscle lost forever Thus the heart of a patient with an infarct must pump a sufficient amount of blood to meet the demands of all organs of the body despite less heart muscle And when the loss of muscle is great the work capacity of the heart is certainly greatly reduced

Therefore the physician should treat all patients with pre infarction angina in the same manner in which he would treat a patient with an acute myocardial infarct but before myocardial infarction occurs The patients should be placed at complete bed rest at home or in hospital for at least 30 days with controlled diet sedatives avoidance of psychic and physical stress oxygen and other measures as needed Remember also that if the patient is hospitalized and develops an infarct soon after admission to hospital he is already in a CCU or a private room where emergency therapeutic measures are immediately available with trained experts in attendance This situation is certainly better for the patient than his having to call and wait for a mobile CCU or to be transported by ambulance or automobile to the hospital *Furthermore very few patients with pre infarction or crescendo angina will develop an infarct anyway if proper therapeutic measures are employed promptly in advance*

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Effects of cardiopulmonary bypass on the jugular venous pulse

The volume of the jugular venous pulse reflects changes in the right atrial pressure contour The technique of cardiopulmonary bypass commonly includes cannulation of the right *atrium and left ventricle* and amputation of the right atrial appendage and thus might be expected to alter the jugular venous pulse Hartman noted reductions in the A wave and X descent following operation for atrial septal defect This reduction even occurred in one patient in whom the atrium was entered but the defect not repaired suggesting that closure of the defect was not responsible for the changes in the jugular pulse

We have noted attenuation of the jugular A wave and X descent in a number of patients undergoing cardiopulmonary bypass for a wide variety of cardiac lesions and have been prompted to review the jugular pulse recordings in 34 of our patients who underwent cardiac surgery

Jugular pulses were recorded by the method of Tavel[1] Tracings were obtained within one month prior to surgery in 29 patients and from one week to ten years postoperatively in 34 patients Preoperative tracings were not available for five patients all of whom had undergone cardiopulmonary bypass. Twenty five of these patients (13 males 12 females mean age 39) underwent surgery which utilized cardiopulmonary bypass for the following diseases mitral stenosis (7) aortic stenosis

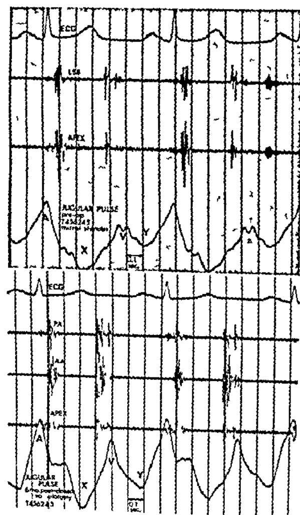


Fig 1 Pre and postoperative jugular venous pulse tracings of a patient undergoing closed mitral valvulotomy

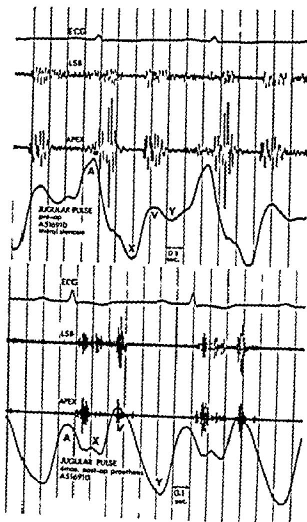


Fig 2 Pre and postoperative jugular venous pulse tracings of a patient undergoing mitral valve replacement

(4) mitral regurgitation (1) aortic regurgitation (5) ventricular septal defect (7) atrial septal defect ( ) idiopathic hypertrophic subaortic stenosis (4) sinus of Valsalva aneurysm (1) left atrial tumor (1) and discrete subaortic stenosis (1) All patients were in sinus rhythm The results of preoperative cardiac catheterization including right atrial pressure (which resembled the jugular venous pulse contour in each case) right ventricular pressure and pulmonary artery pressure were available for 4 cases

The heights of the A wave and V deflections were determined using the lowest point on the tracing as baseline and expressed as the ratio A V The depths of the X and Y troughs were determined using the highest point on the tracing as baseline and expressed as the ratio X Y

A V was 1 1 or greater in all patients preoperatively Postoperatively 1 of the 75 patients who underwent bypass showed reversal of this ratio to less than 1 1 None of the five patients who underwent surgery without bypass showed similar reversal. Mean A V was 1 9 1 preoperatively and 0 9 1 postoperatively ($p < 01$) A V was not significantly different postoperatively in those not undergoing cardiopulmonary bypass

X Y was 1 1 or greater in all but one patient a man with acute aortic regurgitation Eighteen of the 75 undergoing cardiopulmonary bypass reversed the ratio to less than 1 1 None operated without bypass showed reversal Mean X Y preoperatively was 1 5 1 and was 0 9 1 postoperatively ($p < 05$) X Y was not significantly different after surgery not using bypass

Exclusion of patients with evidence of right ventricular or pulmonary hypertension did not alter the significance of the e changes.

Fig 1 illustrates pre and postoperative jugular venous pulse tracings in a 30-year old woman with mitral stenosis who underwent closed mitral valvulotomy The preoperative tracing shows an A wave larger than the V wave and the X descent deeper than the Y No significant change in these ratios occurred postoperatively Fig 2 illustrates typical changes in the jugular pulse following cardiopulmonary bypass surgery This 47 year-old woman with mitral stenosis

had a normal jugular pulse tracing preoperatively and clearly showed diminution in the amplitude of the A wave relative to the V wave and loss of X descent relative to Y descent postoperatively Changes similar to those illustrated were appreciable at the bedside in a number of patients

Cardiopulmonary bypass surgery thus appears to alter both atrial contraction (diminution of the A wave) and atrial relaxation (diminution of the X descent) Several possible mechanisms can be postulated for these changes (1) the actual loss of atrial tissue at bypass is small but it is conceivable that contraction patterns could be altered or that electrical conduction within the right atrium was disturbed (2) adhesions may have formed around the atrium impairing both contraction and relaxation (3) the morphologic changes could have resulted from relative accentuation of the V wave and Y descent suggesting tricuspid regurgitation but the absence of tricuspid murmurs and the regularity of the finding mitigate against this (4) as the diminution of A waves after surgery was independant of pre existing right ventricular hypertension successful surgical repair of the underlying cardiac lesion would not in itself account for the changes noted and (5) rather than directly affecting the atrium the changes noted here could have been due to some nonspecific effect of cardiopulmonary bypass surgery on right ventricular compliance

These data indicate that open heart surgery using cardio pulmonary bypass techniques produces alterations in the right atrial and jugular venous pulse relationships resulting in the relative enhancement of the V wave and Y descent relative to the A wave and X descent Regardless of the exact mechanism of production of these changes they do preclude the use of the jugular pulse to assess postoperative closure of atrial septal defects Furthermore our data indicate the need for extreme caution in the use of the jugular pulse to diagnose tricuspid regurgitation after cardiopulmonary bypass

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Letters to the Editor

Systolic clicks and murmurs

To the Editor

Dr Haas has attributed the decrease and/or disappearance of midsystolic click late systolic murmur (MSC LSM) in the third trimester of pregnancy to decreased peripheral vascular resistance However the most typical response of the MSC LSM to decrease in peripheral vascular resistance is for the systolic murmur to occupy more of systole and for the systolic click to move earlier in systole I have observed these auscultatory changes in a 25 year old female during the second and third trimester of pregnancy which were associated with increase as compared to pre pregnancy in left ventricular end systolic and end-diastolic diameters determined by echocardiography There was also a marked decrease in her awareness of palpitations and in the frequency of clinically observed atrial and ventricular extrasystoles but there were no observable changes in the duration or extent of the mitral valve prolapse by echocardiography These observations suggest increase in blood volume as the likely cause of changes in pregnancy in MSC LSM

It is also mentioned that non invasive clinical maneuvers can indicate the changes in volume of mitral regurgitation The presence or intensity or duration of systolic murmurs are not reliable guides to the extent of or even the presence of angiographically determined mitral in ufficiency

These comments do not detract from the pertinence of the author s observations or his conclusions regarding clinical management of these patients during pregnancy

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Reply

To the Editor

I wish to thank Dr Sasse for his letter concerning my article "The effect of pregnancy on the midsystolic click and murmur of the prolapsing posterior leaflet of the mitral valve which appeared in the September 1976 issue of AMERICAN HEART JOURNAL

Dr Sasse has apparently interpreted the article to imply that the decrease and/or disappearance of the midsystolic click late systolic murmur in the third trimester of pregnancy is due completely to a decrease in peripheral vascular resistance I agree with Dr Sasse as to the change in the intensity of the murmur and the shift of the midsystolic click to early systole with a decrease in peripheral vascular resistance alone If one reads the article completely he will see that our interpretation for the auscultatory phenomenon and its change in pregnancy is related to a combination of increase in blood volume that occurs with gestation which probably realigns the mitral valve apparatus by increasing the left ventricular end-diastolic volume and the long axis of the left ventricle together with a reduction in peripheral vascular resistance Perhaps the change in volume is the more important of the two?

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Survival of elderly patients after pacemaker implant

To the Editor

In the April 1976 issue of AMERICAN HEART JOURNAL Dr Amikam and co-workers report on favorable long term follow up survival rates in elderly patients with a permanent cardiac pacemaker implanted at an age of more than 70 years Emphasizing the beneficial effects of pacemaker implantation in this age group in terms of prolongation of life and improvement of its quality the authors point out that this aspect of pacemaker therapy has so far been paid little attention in the literature

In this context we should like to refer to our results on a series of 1 708 pacemaker patients Although the cumulative survival rate was slightly less favorable in the patient group as a whole as well as in the elderly subjects than the corresponding figures of the cited study the relative survival rate (ratio of the actual and the expected survival rate of the same age group in the general population) in patients beyond 80 years of age was found to be higher than in the age groups of 60 to 80 years after 9 years of follow up Taking into account that according to the results of a questionnaire a high percentage of previously disabled patients were capable of looking after themselves and their households after having a pacemaker implanted we can confirm the justification of permanent cardiac pacing even at a very advanced age

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Book reviews

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This is an important book on an important subject The results of surgery on infants and children with congenital cardiac defects have interested parents and doctors for a long time Now that many years have passed since successful cardiac surgery has been introduced it is possible to learn the results of cardiac surgery The hemodynamic results functional state of the patients rate of survival and other aspects of surgical operations are answered in part The reader will find the book to contain papers which are short but succinct and others which contain data related to only short postoperative follow up The short time follow up of patients is well known The long time results are important also and possibly more important The medical literature abounds with data for the first hours days or weeks after surgery But what about 10 20 or more years later? A future edition should be concerned almost entirely with long time follow up data The volume is nicely bound and the publication format is very good This is an important and useful book

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This book on congestive heart failure (CHF) reviews one of the most important and highly fatal diseases in medicine The mechanism and pathogenesis of this disease state have not yet been fully defined The many manifestations have been described but the precise pathophysiologic factors responsible for the entire syndrome is yet to be described This book edited by Mason describes many of the manifestations of CHF These include structural changes in the myocardium hemodynamic and other physiologic changes biochemical abnormalities enzymatic changes energetics biophysical alterations and clinical and other changes found in CHF Treatment is discussed including the management of edema arrhythmias and even counterpulsation This reviewer would consider the book to represent an over attempt to be all inclusive so that those interested in any specific aspect in detail would find the presentation wanting For example the discussion of repair of ventricular septal defect from a clinical point of view is a complex problem such as differential diagnosis etiology of the CHF etc Regardless the reader will find a great deal of important information concerning the state of knowledge briefly described for the busy clinician and physiologist The book should prove useful and valuable The bibliography is highly selected and includes mainly recent publications Those interested in any aspect of CHF will find it valuable to exhaustively review and study all (if possible) previous publications which contain important data and concepts CHF in cardiology is a complex and most difficult problem to comprehend fully It has been studied for many years by many people This book reviews very well some of the more recent investigations of a most important problem in cardiology

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The Fourth Hahnemann International Symposium on Hypertension was concerned primarily but not only with the role of the central nervous system (CNS) in the regulation of arterial blood pressure This aspect of blood pressure regulation is too often forgotten Many of the most effective antihypertensive agents function through their influence on the central nervous system The main topics discussed include emotional factors release of renin through nervous system action and centrally acting antihypertensive agents Every physician who manages arterial hypertension will find this publication of the symposium to be most profitable to review The contributors are worldwide in origin This is a very useful book on a most important subject Since the means are now available to control blood pressure all physicians should be well acquainted with these means This book contains a great deal of useful information for clinicians as well as for pharmacologists

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This is an excellent summary of two centuries of medicine in the USA The authors are capable physicians teachers and authors and, as would be expected, they have published an interesting and accurate review of the important historical developments made in American medicine This book contains a review of all aspects of medicine It is truly an extensive and excellent historical review The book is divided into three parts (1) The First Century 1776-18 6 (2) Period of Scientific Advances 18 6-1946 and (3) Period of Explosive Growth 1946-19 6 Those who have been active in medicine for many years will certainly appreciate this book most whereas the younger physician and medical student will learn a great deal about the history of American medicine This book is worth owning

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Book reviews

The Child With Congenital Heart Disease After Surgery *Edited by B S Langford Kidd M D and Richard D Rowe M D* Mount Kisco New York 1976 Futura Publishing Company 466 pages Price $29 50

This is an important book on an important subject The results of surgery on infants and children with congenital cardiac defects have interested parents and doctors for a long time Now that many years have passed since successful cardiac surgery has been introduced it is possible to learn the results of cardiac surgery The hemodynamic results functional state of the patients rate of survival and other aspects of surgical operations are answered in part The reader will find the book to contain papers which are short but succinct and others which contain data related to only short postoperative follow up The short time follow up of patients is well known The long time results are important also and possibly more important The medical literature abounds with data for the first hours days or weeks after surgery But what about 10 20 or more years later? A future edition should be concerned almost entirely with long time follow up data The volume is nicely bound and the publication format is very good This is an important and useful book

Congestive Heart Failure Mechanisms Evaluation and Treatment Edited by Dean T Mason M D New York 1976 Yorke Medical Books 448 pages $35 00

This book on congestive heart failure (CHF) reviews one of the most important and highly fatal diseases in medicine The mechanism and pathogenesis of this disease state have not yet been fully defined The many manifestations have been described but the precise pathophysiologic factors responsible for the entire syndrome is yet to be described This book edited by Mason describes many of the manifestations of CHF These include structural changes in the myocardium hemodynamic and other physiologic changes biochemical abnormalities enzymatic changes energetics biophysical alterations and clinical and other changes found in CHF Treatment is discussed including the management of edema arrhythmias and even counterpulsation This reviewer would consider the book to represent an over attempt to be all inclusive so that those interested in any specific aspect in detail would find the presentation wanting For example the discussion of repair of ventricular septal defect from a clinical point of view is a complex problem such as differential diagnosis etiology of the CHF etc Regardless the reader will find a great deal of important information concerning the state of knowledge briefly described for the busy clinician and physiologist The book should prove useful and valuable The bibliography is highly selected and includes mainly recent publications Those interested in any aspect of CHF will find it valuable to exhaustively review and study all (if possible) previous publications which contain important data and concepts CHF in cardiology is a complex and most difficult problem to comprehend fully It has been studied for many years by many people This book reviews very well some of the more recent investigations of a most important problem in cardiology

Regulation of Blood Pressure by the Central Nervous System Edited by Gaddo Onesti M D Michael Fernandes M D and Kwan Eun Kim M D New York 1976 Grune & Stratton Inc 484 pages $36 50

The Fourth Hahnemann International Symposium on Hypertension was concerned primarily but not only with the role of the central nervous system (CNS) in the regulation of arterial blood pressure This aspect of blood pressure regulation is too often forgotten Many of the most effective antihypertensive agents function through their influence on the central nervous system The main topics discussed include emotional factors release of renin through nervous system action and centrally acting antihypertensive agents Every physician who manages arterial hypertension will find this publication of the symposium to be most profitable to review The contributors are worldwide in origin This is a very useful book on a most important subject Since the means are now available to control blood pressure all physicians should be well acquainted with these means This book contains a great deal of useful information for clinicians as well as for pharmacologists

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Editorial

Congestive heart failure is not due to low cardiac output *per se*

George E Burch M D
New Orleans La

The medical literature is replete with studies statements and conclusions that congestive heart failure (CHF) is due to a low cardiac output And in recent years these statements have been interpreted to mean pump failure reflection of low or reduced cardiac output In fact cardiac output is almost always the important measurement cited in the medical literature to establish or to indicate the existence of pump failure The idea that low cardiac output alone is responsible for the expression of pump failure CHF cannot be entirely correct as I have indicated previously Low cardiac output may reflect pump failure when it is properly considered in light of the entire physiologic state of the heart and circulation at the time it is measured But low cardiac output does not in itself indicate nor is it alone pathognomonic of CHF

It is too frequently forgotten that although man has one heart the heart is composed of two separate and distinct pumps namely the right and left ventricles Each pump is separated by extremely complex vascular systems which are controlled by complex and poorly understood nervous and humoral systems with equally complex organ systems to which the blood must be supplied by these two separate pumps As indicated previously these two distinct pumps and the intervening vascular systems must be extremely delicately synchronized and integrated functionally in the normal state of health for normal function of the heart (with its two pumps) and circulation One of the most impressive aspects of cardiac function concerns the excellent and elegant physiologic regulatory mechanisms by which each ventricle normally ejects the same volume of blood in spite of the fact that they are separated from each other by extremely complex vascular systems macro and microcirculations which influence the functions of the two pumps This normal delicate synchronization of the time course of function of each pump is not dependent entirely upon hemodynamic factors but more importantly depends upon the proper function of the nervous systems with delicate complex sensing devices receptors and responding integrating devices (CNS pathways and centers and peripherally located ganglia) and neural and humoral circuits and regulators Proper function of these systems is necessary to assure synchronized right and left heart function even under rapidly changing and stressful circumstances of the organism and demands placed upon the two pumps and the peripheral blood vessels Unfortunately these synchronizing factors and nerve functions have received extremely little attention and are inadequately known and poorly understood Yet without such knowledge pump failure is being simply equated with a low cardiac output The importance of extremely close and delicately interrelated time courses of function of the right and left ventricles (the two pumps) has been clearly indicated[1] However this has been ignored by most investigators and clinicians The roles of baroreceptors volume receptors stretch

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Announcements

XIX International Congress on Occupational Health

The 19th International Congress on Occupational Health will be held September 25 through 30 1978 in Dubrovnik Yugoslavia The Congress will be organized by the Yugoslav Association on Occupational Health and the Institute for Medical Research and Occupational Health For further information please contact Prof M Sarić Chairman Organizing Committee M Pijade 158 P O B 291 YU-41001 Zagreb Yugoslavia

First International Congress on Cardiac Rehabilitation

The First International Congress on Cardiac Rehabilitation sponsored by the International Society of Cardiology Council on Rehabilitation will be held in Hamburg Germany September 12 through 14 1977 The purpose of this Congress will be to critically display the present concepts of cardiac rehabilitation and to collect information on the ongoing activities For further information please contact Prof Dr Med Kurt Konig Secretary of the Congress Herz Kreislauf *Klinik Waldkirch Kandelstrasse 41 Postfach 270 D 7808* Waldkirch Federal Republic of Germany

Jane Nugent Cochems Competition

The University of Colorado School of Medicine announces the Fourteenth Annual Cochems Competition A prize of $2 500 will be awarded to the author of the best paper concerning Thrombophlebitis and Basic Vascular Problems It should be concerned with the mechanisms or processes of vascular disease particularly thrombosis but not restricted to it Eligibility is limited to physicians subject to U S income tax regulations Entries must be received in triplicate on or before November 30 1977 Inquiries regarding the competition and all manuscripts should be submitted to the Dean School of Medicine University of Colorado Medical Center 4200 East Ninth Ave Denver Colo 80262

XIII World Congress of the International Cardiovascular Society

The XIII World Congress of the International Cardiovascular Society will be held from August 30 to September ? 1977 at the Keio Plaza Inter Continental Hotel, Tokyo Japan For registration forms and further information please contact Masahiro Saugusa M D Secretary General 3023 7 Chome Roppongi Minato ku Tokyo 106 Japan

Echocardiography in Hawaii

The Maui Intercontinental Hotel on the island of Maui, Hawaii will be the site of this symposium sponsored by the Honolulu Medical Group Inc and the John A Burns School of Medicine University of Hawaii from August 15 through August 19 1977 Five one half day sessions presented by authorities of international prominence are designed to enhance the interpretive skills of physicians engaged in echocardiography Tuition is $350 00 Approval for AMA Credit Category 1 can be obtained

For further information write Vincent E Friedewald Jr M D Program Director The Honolulu Medical Group Inc 550 S Beretania St Honolulu Hawaii 96813

Workshop in Echocardiography

A seminar entitled A Workshop in Echocardiography *will be held on September 1 through 4* 1977 at the Pinel le Resort Hotel at Lake Lanier Islands Buford Ga (40 minutes north of Atlanta) The seminar will be directed by Louis Evan Teichholz M D Associate Chief of Cardiology Mount Sinai Medical Center and Associate Professor of Medicine Mount Sinai School of Medicine New York City For further information regarding this seminar please contact Ms Billie N Chiles Tampa Tracings P O Box 1245 Tarpon Springs FL 33589

today adds nothing to the knowledge needed to understand the mechanism or existence of the complex pathophysiologic phenomena of CHF Unfortunately measurements of cardiac output are erroneously used alone to investigate such phenomena Furthermore the present methods for such measurements are too insensitive to detect the slight changes which can occur to produce CHF acutely or chronically The same situation described above for acute CHF such as with ischemic myocardial disease applies as well to chronic CHF

As stated above the remarkable aspect of the two pump function is how well the two pumps of the heart are regulated and synchronized normally But what are the remarkable controlling mechanisms? When cardiac output is measured in the presence of a smooth well synchronized right and left heart pumping function some interesting information may be obtained but of what value is this information in understanding the pathophysiology or cause for the complex pathophysiologic state of CHF at any given time? Clinically and by simple bedside observation one knows when a smooth normal well synchronized circulation and elegant right and left heart functional synchronism exist When asynchronism develops the syndrome of CHF follows and any good clinician observes early and readily the existing CHF and the fact that the right and left heart pumps are not functioning synchronistically It behooves investigators and clinicians to determine why the dysfunction exists and to institute proper therapeutic measures to reestablish good synchronistic right and left heart pump function The degree of CHF depends on the extent or degree of asynchronism and reasons for this asynchronism or dyssynchronism

If the mere presence of a low level of cardiac output were unfavorable and resulted in CHF all normal people would develop CHF at 3 A M while sound asleep in bed when their circulation is at its lowest level of activity Furthermore CHF should improve with exercise of the patient or with exposure of the patient to a hot and humid environment since both factors always increase cardiac output but this is not the case

Vigorous exercise increases cardiac output in the presence of CHF but the CHF worsens Likewise a hot and humid environment worsens CHF without increasing very much if at all the need for more blood supply to tissues to meet metabolic requirements In fact a patient in CHF can be easily killed by a hot and humid environment CHF worsens under such circumstances in large part because the asynchronism of the two ventricles is worsened Merely increasing cardiac output does not correct the asynchronism present in CHF The hot environment and vigorous exercise do not influence the two pump synchronism and the complex phenomena responsible for synchronistic function of the two cardiac pumps They merely reveal the existence of poor cardiac function A normal well synchronized right and left heart pump would respond well to exercise and exposure to a hot and humid environment and there would be no CHF Of course if total muscle contractile force is poor due to myocardial pathology and loss of muscle then even with adequate and elegant synchronization of two pump function there would be pump" failure But would the failure be different? Digitalis a cardiotonic agent will stimulate the myocardium to increase its work and power output if the muscle is not too extensively damaged *to* respond

The intervening pulmonary *vascular system* and peripheral vascular system play an extremely important role in maintaining the necessary delicate elegant synchronisms of function between the two pumps of the human heart the right and *left ventricles* independent of direct innervation of the heart (the two pumps) That this is true is best supported by the fact that the transplanted heart can function fairly well even with interruption of central nervous system connections but dependent on elastic and hemodynamic phenomena

In an attempt to explain in simple terms what is meant by the relatively little value of low cardiac output alone and the extreme importance *of elegant and* fine synchronism of the right and left ventricular pumps and the intervening pulmonary and systemic circulations and nervous *system* with their complex and little studied and little known sensors receptors effectors integrating nerve centers etc these concepts will be compared to an automobile engine

For an automobile engine to function well engineers and designers have introduced timing devices wire and electric circuits carburetors injectors pistons well *fitted into* cylinders and other well known devices to assure a well synchronized function of the time course of firing of

reflexes, chemoreceptors, and other complex and little known and little understood neurologic *hemodynamic, and humoral* regulatory phenomena are most important in the closely *interrelated*, delicate and constant functional synchronism of the two pumps Some aspects of the delicate role of the peripheral and central nervous systems have been published [1] But hemodynamic technics available and used today are too crude to provide useful information for the elucidation of the delicate two pump synchronization necessary for normal over all cardiac function

A simple example and well known clinical state which displays the importance of close physiologic relationships and the need for a constant delicate synchronism of right and left heart pumping function is the acute CHF that occurs during an episode of angina pectoris, acute coronary insufficiency, or myocardial infarction These ischemic cardiac states are left ventricular disease states Ischemic heart disease is rarely a disease of the right ventricle Angina pectoris and myocardial infarction of the left ventricle occur acutely and when either occurs the left ventricular cardiac output may decrease suddenly and this decrease may be only 1 to 2 c c per stroke This volume change is too small to be measured by any of the existing hemodynamic and cardiac *output recording* technics even the most sophisticated ones and even though employed by the best technologists When this 1 to 2 c c decrease in left ventricular stroke volume occurs and the right ventricle continues to pump 1 to 2 c c more blood per heart beat into the pulmonary vascular system than the left ventricle can pump out of the lungs into the systemic circulation (and venoconstriction associated with left ventricular CHF squeezes blood through the right pump into the lungs) then pulmonary vascular congestion or pulmonary edema rapidly develops For example if the heart rate is 100 beats per minute 100 to 200 c c more blood will be pumped per minute into the lungs by the right ventricle than is removed or pumped from the lungs per minute by the left ventricle Within 2 to 5 minutes the vessels of the lungs are engorged with blood and acute pulmonary congestion and acute pulmonary edema follow These are manifestations of the fact that the delicate synchronism of the right and left pumps and the peripheral venous system have been disturbed The patient rapidly becomes moribund is breathless is *frothing* at the mouth with bloody edema fluid and displays all sorts of arrhythmias and may even die before the necessary delicate synchronism and function of the right and left ventricles and peripheral vascular system can be reestablished either spontaneously or with the aid of proper therapy [1, 4] By this time profound changes in the intervening peripheral circulatory systems have occurred Therapy is achieved in part by reducing venous return to the right ventricle and in turn blood flow to the lungs or by reducing the stimulation of the sick left ventricle and the engorged pulmonary veins A less desirable procedure could be at times to stimulate the sick left heart to pump more blood and increase its contractility But, at times that would be like 'whipping a dying horse Therapy could also consist of an effort to reestablish blood flow to the ischemic areas of the left ventricle with nitroglycerin to add further contracting muscle to each left ventricular heart beat so that its stroke volume increases sufficiently again to remove the extra blood which is over engorging the pulmonary vessels The baroreceptors volume receptors stretch reflexes special nerve sensors smooth muscle *in* all the complex blood vessels and microcirculation and local humoral factors must all be involved in the dysfunctional state of the pump and also in its restoration to normal function What these factors are and how much of a role each plays at any one time are unknown and to study and learn each factor qualitatively *and* quantitatively along with their interrelationships from heart beat to heart beat *for each* ventricle and the intervening circulation would be a most *complex* and difficult task But these many factors must be present and must influence the *two* pump function The many complex synchronizing readjustments to *any change in function* of the two pump system take time The hemodynamic humoral and nervous controlling factors must be complex

Thus an acute episode of myocardial ischemia is an example of a disturbance in synchronism of two important pumps which are separated by live and extremely complex active circulatory phenomena And these factors and physiologic phenomena are evidently independent to a great extent of the level of total cardiac output whether it be high or low

The mere measurement of cardiac output or stroke volume by the crude methods available

the peripheral nerve ganglia and the central nervous system must be important Disease of any of these parts must have a detrimental influence on the synchronization of the two heart pumps and other aspects of cardiac function For example we have found that the Coxsackie B virus will damage sympathetic ganglia important centers necessary for proper integration of nerve function Grodums and Zbitnew[7] found that the *herpes simplex* virus will also damage nerve ganglia of the heart These ganglionic lesions must disturb cardiac function for it is well known that the major role of the nervous system is to integrate organ functions of a complex organism such as man

It has been shown[8] from a study of the ECG at the Charity Hospital over the past 40 years how lesions of the central nervous system will alter the ECG significantly and even diagnostically This has been confirmed by others[9-12] CNS lesions will also produce anatomic cardiac lesions in the hearts of mice[13] Tachycardias with fear or psychic tension cardiac arrhythmias angina pectoris myocardial infarction associated with stressful central nervous system states as well as many other well known clinical cardiac states support the importance of the role of the nervous system in elegant normal cardiac function Disturbances of these regulatory phenomena result in cardiac dysfunction

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fuel delivered to the respective cylinders to produce good 'pumping' or power output" of the engine If these regulating devices are all functioning properly and are well synchronized, engine function will be good regardless of speed of function or rate of power output For example, the auto engineer will not claim that when the speed of the automobile is at 65 miles per hour its power output is high and it is functioning well but that it is suffering from pump' failure or "power failure when its speed is reduced to 5 miles per hour and its power output is much less From his studies of the well synchronized engine and time course of firing of each cylinder, he will know and find that there is no failure at all at any speed or power output In fact, the auto engineer usually studies the performance of the engine when the automobile is at a standstill and motionless and when work and power output of the engine are zero

But, if the distributor of the automobile and other timing and synchronizing devices are not working well and the engine is not well synchro nized the engineer may still run the automobile at 65 miles per hour or 5 miles per hour or at a standstill with the power output of the automo bile at zero and he will know that the engine is failing to pump ' or is producing ' power output in a reduced amount or is not pumping or functioning well The time course of firing of the respective cylinders is disturbed Measuring the speed of an automobile or its power output alone would certainly not indicate whether or not the engine was functioning well or the reasons why it was or was not more studies than power output alone are necessary The auto engineer must locate the trouble and therapeutically correct it The engine will then again function well and the firing of fuel in the cylinders will be elegantly synchronized and the engine will be compensated or cured of power failure Surely, the power output of an engine can be low, or the engine can fail even when firing of fuel in the cylinders is well synchronized if compression in the cylinders is low The same is true for the heart when heart muscle is excessively lost or diseased In such instances even with excellent synchronization of all regulating mechanisms cardiac work and output are inadequate or low even with stimulation such as with digitalis Elegant synchronization will not increase cardiac output when the contractile ability of the heart muscle is impaired or the muscle is too sick to work adequately

But, the automobile engine is simple in compar ison to the right and left heart pumps of man People designed the automobile engine and installed the few, yet important integrating devices to assure piston synchronism and good engine function But man did not design the integrating and other 'devices which synchro nize the function of the right and left ventricles of the heart of man This was done for him and it behooves the physician to study, try to under stand, and try to learn precisely what the distur bances are in CHF and how to reestablish good function with the existing limited knowledge and therapeutic agents The integrating and synchro nizing mechanisms must be fully learned for the benefit of the management of CHF and to under stand the regulation and integration of function of the two pumps of the heart Surely, when parts of the myocardium fail to contract or fail to contract in proper time sequence then poor heart function follows and all sorts of dyschronitic states develop The clinical state of CHF becomes readily recognized at the bedside by means of simple examinations

The peripheral and central nervous systems are of paramount importance in smooth two pump synergistic function and good cardiac function The large heart and silent isolated areas of heart dysfunction partial contractions improper time sequence of myocardial conduction and myocar dial contraction in all respects are among the many factors responsible for poor or inadequate synergistic and synchronistic two pump heart function and even for the proper functional role of the peripheral vascular (pulmonary and systemic) systems necessary for the elegant synergistic and synchronistic two pump function When CHF is present, these peripheral vessels reflect it by the development of abnormal mani festations including renal dysfunction (not primary renal disease) with the resultant accumulation of water and electrolytes etc The peripheral blood vessels as previously shown [3] are abnormally constricted in CHF This certainly reflects peripheral vascular changes of utmost importance and is further evidence of hemody namic and vascular dysfunction which could be responsible in part for dyssynchronism

Lesions or functional disturbances of the nerve fibers end organs sensors integrating centers of

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Clinical communications

An abnormal early diastolic impedance waveform A predictor of poor prognosis in the cardiac patient?

Marcos U Ramos, M D *
Minneapolis Minn and Boston Mass

The search for non invasive methods to evaluate ischemic heart disease has received much recent attention due to the difficulties in evaluating the extent of myocardial damage and the morbidity most invasive procedures have As a result of this interest there are many new methods and instruments available for the non invasive evaluation of different cardiovascular functions Some exist on a research basis and few of them are available to the clinician on a limited basis

For the last three years this laboratory has been using the Minnesota Impedance Cardiograph along with the electrocardiograph in patients admitted to the Coronary Care Unit, and later during their cardiac rehabilitation process The first resting impedance recording was done as part of the initial work up of the patients admitted with an acute myocardial injury Serial recordings while in supine position were also made during the first three or four days after admission

During the course of this study the impedance cardiographic tracing from some patients showed an unusual early diastolic waveform not observed in most patients and never recorded on normal subjects Repeated recordings on these patients under similar conditions revealed the consistent presence of this aberrant early diastolic wave form

The purpose of this report is the retrospective analysis of the clinical course and eventual outcome of 30 patients in whom this abnormal waveform was recorded This population of patients is also compared with the 51 patients in whom this abnormal waveform was not present Both groups were admitted to the Coronary Care Unit with acute cardiovascular illnesses during the same period of time

Methods and procedures

More than 400 impedance tracings were recorded from the 81 patients successively admitted to the Coronary Care Unit with diverse acute cardiovascular illnesses acute myocardial infarction acute coronary ischemia and severe congestive heart failure The only selection factor was the availability of the investigator and equipment at the time of their admission The recordings were obtained using the Minnesota Impedance Cardiograph Model 304

This system uses four aluminized mylar tape electrodes placed as shown in Fig 1 Between the outer electrodes (Numbers 1 and 4) a constant sinusoidal current of 4 mA with a frequency of 100 KHz is applied to the thoracic region The second and third electrodes (Numbers 2 and 3) limit the thoracic cavity and offer information regarding the electrical potential changes of the passage of the current These changes reflect the impedance changes of the encompassed region

Simultaneous recordings of the first derivative of the thoracic impedance change (dZ/dt) phonocardiogram and a non diagnostic ECG tracing were displayed by the recorder (Fig 2) The resting recordings were taken following a 20

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Table I Complications in patients in Groups A and B

Complications	Impedance waveform	
	Group A normal	Group B abnormal
Ventricular arrhythmias	6	5
Hypotension	6	9
Cardiogenic shock	1	2
Congestive heart failure	5	11
Complete heart block	1	0
Bradycardia	1	7
Persistent angina	2	9
Cardiopulmonary arrest	0	4
None	28	7
ECG diagnosis classification		
WNL (within normal limits)	1	2
NDX (non diagnostic)	7	4
SI (subendocardial ischemia)	10	4
AMI (anterior myocardial infarction	11	13
IMI (inferior myocardial infarction)	14	4
PMI (posterior myocardial infarction)	8	3

The two remaining patients were admitted in congestive heart failure secondary to valvular heart disease Eighteen of these patients died during the five month follow up six of them died during the initial admission to the hospital

Retrospective analysis of the data in terms of the presence or absence of the abnormal impedance waveform shows a clear difference between these two groups Group A patients without abnormal waveform (N = 51) and Group B patients showing the abnormal waveform (N = 30) The observed difference in their clinical course is displayed in Table I This table shows the incidence of complications in the two groups From this it is clear that patients in Group B (showing the abnormal waveform) belonged to a population with poorest prognosis This difference was not evident on admission or early during their hospital stay Their mean age (63 8 years in Group B) did not differ significantly from the mean age of the total population of 81 patients This table shows a clear difference in the incidence of congestive heart failure bradycardia persistent angina and cardiopulmonary arrest between the two populations The higher incidence of these parameters in Group B (patients with abnormal impedance waveform) is clear It is interesting to observe that the incidence of ventricular arrhythmias is similar in both groups The incidence of hypotension is slightly higher in Group B

The distribution of electrocardiographic diagnoses among the two groups is different as Table I shows While 18 of the patients in Group A demonstrated electrocardiographic patterns, which are usually associated with a less grave prognosis, i e WNL NDX SI, 25 of them showed infarctions in the anterior, and inferior walls where the incidence of ventricular aneurysms and A V blocks is much higher[4] The distribution among Group B is similar throughout the whole spectrum except for a marked peak in the category of anterior myocardial infarction which was shown by 13 of the 30 patients in Group B

Fig 3 depicts the eventual survival of these two groups in terms of the New York Functional Classification While 90 per cent (46/51) of the patients without the abnormal waveform (Group A) were eventually classified into Class I and II 66 per cent (20/30) of Group B were eventually classified into Class III and IV (χ = 28 6 P < 001)

The different distribution of the 18 patients who eventually died is even more impressive and highly significant (χ × 26 7 P < 001) Sixteen of them (89 per cent) belonged to Group B and only two out of 51 patients in Group A died The one patient under Class II a 56 year old woman who was discharged 25 days after an anterior myocardial infarction The clinical course was uneventful She was readmitted two days after discharge this time with an acute posterior myocardial infarction She died after cardiac arrest two hours post admission The one patient in Class III was an 80 year old man admitted with an inferior myocardial infarction who died of cardiogenic shock two days after admission

Discussion

The studies by Kubicek Patterson and associates[5, 6] have culminated in the development of an electrical impedance device referred to as the Minnesota Impedance Cardiograph This system attempts to assess changes in stroke volume by means of the changes in the transthoracic electrical impedance which occur during the cardiac cycle Several authors[7] have observed that as a result of the systolic ejection there is a small but measurable drop in the electrical impedance of the thoracic region There is evidence demon

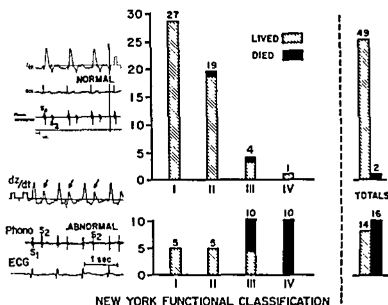


Fig 3 This illustrates the eventual outcome of both Groups A and B in terms of the New York Heart Association Functional Classification Notice that data from Group A (normal impedance waveform) *displayed at the top* show that most of the patients were eventually classified under Class I and II Only two of the 51 died Comparison of these data with the one obtained on Group B (patients with abnormal waveform) *shown at the bottom* makes clear that Group B belonged to a group with the poorest prognosis since 66 per cent were eventually classified under Class III and IV Observe that 16 of the 31 died

strating that the first derivative of the thoracic impedance change (dZ/dt) is proportional to the systolic ejection as measured by aortic flow meters and its height correlates linearly with the changes in the systolic ejection In a recent study where the impedance cardiac output was compared with the Fick method a correlation coefficient of 0 91 was found for the stroke index calculated by these two methods

A typical impedance cardiographic tracing is shown in Fig 2 The temporal sequence of events show the cardiac cycle being initiated by the QRS complex followed by the first heart sound (S) At the time of the highest amplitude of S_1 there is a steep upswing of the dZ/dt curve which crosses the baseline and achieves a maximal height Following this peak there is a rapid fall in dZ/dt achieving its lowest point concurrent with the second heart sound (S) This downswing of the dZ/dt along with the S mark the end of systole During the diastolic phase minimal wandering of the dZ/dt tracing is observed until the next cardiac cycle

The abnormal early diastolic impedance wave form we are describing is a sharp upward deflection in the early diastolic phase (Fig 4) Following the second heart sound (S_2) there is a sharp upswing of the impedance tracing achieving its peak approximately 150 msec after the second heart sound The presence of this abnormal wave form in the patients reported here was persistent both in supine position and during exercise During exercise this abnormal impedance wave form increased in height (Fig 5) and disappeared after sublingual administration of nitroglycerin (Fig 6) This waveform has not been observed in normal subjects either at rest or during heavy exercise

A detailed description of the time relationship of the impedance waveform and the events in the cardiac cycle is contained in a report by Lababidi and colleagues [2] It is interesting to note that in his population of normal subjects and patients only ten of the latter with mitral stenosis showed a small upward deflection of the impedance wave form in the early diastolic phase (0 point) The peak of Lababidi s 0 point occurred 150 msec after the second heart sound and coincided with the opening snap Unfortunately no information is given regarding any changes in amplitude related to exercise or nitroglycerin administration The prognostic implications reported here have not been reported before

The abnormal waveform described in this

Table I Complications in patients in Groups A and B

Complications	Impedance waveform	
	Group A normal	Group B abnormal
Ventricular arrhythmias	6	5
Hypotension	6	9
Cardiogenic shock	1	2
Congestive heart failure	5	11
Complete heart block	1	0
Bradycardia	1	7
Persistent angina	2	9
Cardiopulmonary arrest	0	4
None	28	7
ECG diagnosis classification		
WNL (within normal limits)	1	2
NDx (non-diagnostic)	7	4
SI (subendocardial ischemia)	10	4
AMI (anterior myocardial infarction)	11	13
IMI (inferior myocardial infarction)	14	4
PMI (posterior myocardial infarction)	8	3

The two remaining patients were admitted in congestive heart failure secondary to valvular heart disease. Eighteen of these patients died during the five month follow up, six of them died during the initial admission to the hospital.

Retrospective analysis of the data in terms of the presence or absence of the abnormal impedance waveform shows a clear difference between these two groups: Group A patients without abnormal waveform (N = 51) and Group B patients showing the abnormal waveform (N = 30). The observed difference in their clinical course is displayed in Table I. This table shows the incidence of complications in the two groups. From this it is clear that patients in Group B (showing the abnormal waveform) belonged to a population with poorest prognosis. This difference was not evident on admission or early during their hospital stay. Their mean age (63.8 years in Group B) did not differ significantly from the mean age of the total population of 81 patients. This table shows a clear difference in the incidence of congestive heart failure, bradycardia, persistent angina and cardiopulmonary arrest between the two populations. The higher incidence of these parameters in Group B (patients with abnormal impedance waveform) is clear. It is interesting to observe that the incidence of ventricular arrhythmias is similar in both groups. The incidence of hypotension is slightly higher in Group B.

The distribution of electrocardiographic diagnoses among the two groups is different as Table I shows. While 18 of the patients in Group A demonstrated electrocardiographic patterns which are usually associated with a less grave prognosis, i.e. WNL, NDx, SI, 25 of them showed infarctions in the anterior, and inferior walls where the incidence of ventricular aneurysms and A-V blocks is much higher.[4] The distribution among Group B is similar throughout the whole spectrum except for a marked peak in the category of anterior myocardial infarction which was shown by 13 of the 30 patients in Group B.

Fig. 3 depicts the eventual survival of these two groups in terms of the New York Functional Classification. While 90 per cent (46/51) of the patients without the abnormal waveform (Group A) were eventually classified into Class I and II, 66 per cent (20/30) of Group B were eventually classified into Class III and IV ($\chi^2 = 28.6$, $P < .001$).

The different distribution of the 18 patients who eventually died is even more impressive and highly significant ($\chi^2 = 26.7$, $P < .001$). Sixteen of them (89 per cent) belonged to Group B and only two out of 51 patients in Group A died. The one patient under Class II, a 56 year old woman who was discharged 25 days after an anterior myocardial infarction. The clinical course was uneventful. She was readmitted two days after discharge, this time with an acute posterior myocardial infarction. She died after cardiac arrest two hours post admission. The one patient in Class III was an 80 year old man admitted with an inferior myocardial infarction who died of cardiogenic shock two days after admission.

Discussion

The studies by Kubicek, Patterson, and associates have culminated in the development of an electrical impedance device, referred to as the Minnesota Impedance Cardiograph. This system attempts to assess changes in stroke volume by means of the changes in the transthoracic electrical impedance which occur during the cardiac cycle. Several authors[10] have observed that as a result of the systolic ejection, there is a small but measurable drop in the electrical impedance of the thoracic region. There is evidence demon

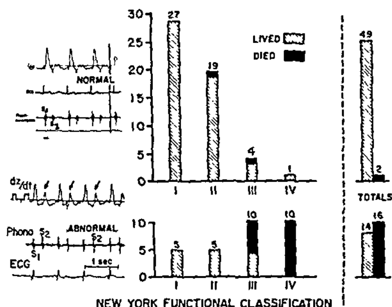


Fig. 3. This illustrates the eventual outcome of both Groups A and B in terms of the New York Heart Association Functional Classification. Notice that data from Group A (normal impedance waveform) *displayed at the top* show that most of the patients were eventually classified under Class I and II. Only two of the 51 died. Comparison of these data with the one obtained on Group B (patients with abnormal waveform) *shown at the bottom* makes clear that Group B belonged to a group with the poorest prognosis since 66 per cent were eventually classified under Class III and IV. Observe that 16 of th 31 died.

strating that the first derivative of the thoracic impedance change (dZ/dt) is proportional to the systolic ejection as measured by aortic flow meters and its height correlates linearly with the changes in the systolic ejection. In a recent study where the impedance cardiac output was compared with the Fick method a correlation coefficient of 0.91 was found for the stroke index calculated by these two methods.

A typical impedance cardiographic tracing is shown in Fig. 2. The temporal sequence of events show the cardiac cycle being initiated by the QRS complex followed by the first heart sound (S_1). At the time of the highest amplitude of S_1 there is a steep upswing of the dZ/dt curve which crosses the baseline and achieves a maximal height. Following this peak there is a rapid fall in dZ/dt achieving its lowest point concurrent with the second heart sound (S_2). This downswing of the dZ/dt along with the S_2 mark the end of systole. During the diastolic phase minimal wandering of the dZ/dt tracing is observed until the next cardiac cycle.

The abnormal early diastolic impedance waveform we are describing is a sharp upward deflection in the early diastolic phase (Fig. 4). Following the second heart sound (S_2) there is a sharp upswing of the impedance tracing achieving its peak approximately 150 msec. after the second heart sound. The presence of this abnormal waveform in the patients reported here was persistent both in supine position and during exercise. During exercise this abnormal impedance waveform increased in height (Fig. 5) and disappeared after sublingual administration of nitroglycerin (Fig. 6).[9] This waveform has not been observed in normal subjects either at rest or during heavy exercise.

A detailed description of the time relationship of the impedance waveform and the events in the cardiac cycle is contained in a report by Lababidi and colleagues.[12] It is interesting to note that in his population of normal subjects and patients only ten of the latter with mitral stenosis showed a small upward deflection of the impedance waveform in the early diastolic phase (0 point). The peak of Lababidi's 0 point occurred 150 msec. after the second heart sound and coincided with the opening snap. Unfortunately no information is given regarding any changes in amplitude related to exercise or nitroglycerin administration. The prognostic implications reported here have not been reported before.

The abnormal waveform described in this

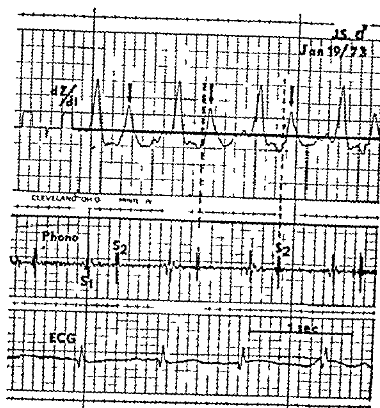


Fig 4 Similar to *Fig 2* this illustrates dZ/dt ECG and phonocardiographic tracing Different from *Fig 1* this tracing shows the abnormal early diastolic impedance waveform Following S this is a sharp upswing of the dZ/dt achieving its peak *(marked by arrows)* approximately 0 150 sec after the second heart sound *(see text)*

report is of greater amplitude and steeper than Lababidi s 0 point None of our patients had organic mitral stenosis Nevertheless the possibility of their having hemodynamic changes similar to the ones found in mitral stenosis left ventricular inflow impairment cannot be ruled out

The etiology of this abnormal waveform is unknown Nevertheless the temporal relation of its appearance with the ventricular rapid filling phase may serve to speculate regarding its etiology

It is known that during this early diastolic phase there is a rapid influx of blood into the ventricles Although passive in nature (no myocardial contraction) sudden and wide changes in pressure create sudden and abrupt fluid movements Rushmer[11] analyzed the slope of the ventricular volume change during this period and found that under normal conditions this early diastolic ventricular filling rate is more rapid than the systolic ejection rate

Under normal conditions following the isovolumic relaxation and the opening of the atrioventricular valves there is a rapid influx of blood from the central veins into the ventricles Gibson and Brown[12] observed that in normal human subjects during isovolumic relaxation there is a rapid and symmetrical outward movement of the left ventricular wall even prior to the opening of the mitral valve In contrast to the above their population of patients with ischemic heart disease showed abnormalities including excessive asymmetric outward movements significantly delayed outward movement and even inward movement of the left ventricular wall during the isovolumic relaxation This last abnormal inward movement was present in patients with poor systolic function

It is reasonable to assume that patients in whom the systolic function and ventricular compliance are so affected will demonstrate severe impairment and inability to handle the load during the rapid filling phase

These hemodynamic abnormalities if severe enough may result in a functional left ventricular inflow impairment similar to Lababidi and colleagues[1] patients in whom a small early diastolic impedance waveform was observed Under these conditions if the end systolic volume is too large the rapid influx of blood in early diastole will be impaired The abrupt pressure changes during isovolumic relaxation will most likely be reflected in the large central veins It is conceivable that these vessels may be acting as a reservoir to absorb the amount of blood the ventricles are unable to handle The abnormal early diastolic impedance waveform may possibly represent the inability of the ventricles to handle the venous return presented to them during early diastole The steep rise of this abnormal waveform may represent the abnormally fast rate of volume change of this compensatory process

Unfortunately no simultaneous invasive and impedance studies were performed on these patients It is only through simultaneous invasive and non invasive studies that the etiology of this abnormal waveform will be clearly elucidated Despite our lack of explanation for its etiology one fact stands clear the presence of such a waveform in retrospect served to identify the patients at higher risk

The appearance of this waveform seems to indicate a pathophysiological derangement rather than a specific disease process i e myocardial infarction since it has been recorded in patients with valvular heart disease severe congestive heart failure and also in the following patient

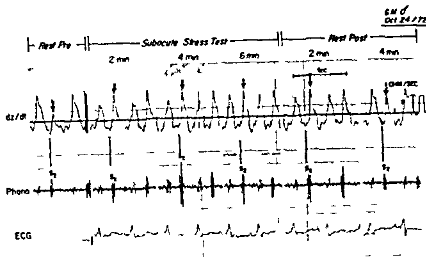


Fig 5 This figure displays the increase in the height of the *abnormal impedance waveform (marked by arrows)* with exercise dZ/dt phonocardiogram and FCG as explained in *Fig 2*

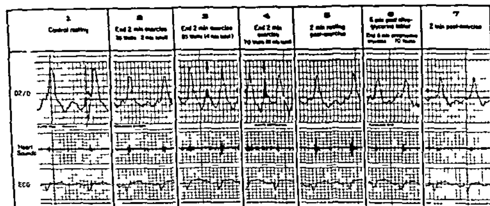


Fig 6 In this figure the abnormal early diastolic impedance waveform appeared after 2 minutes of bicycling at a work load of 53 watts (Phase 3) At a work load of 0 watts the abnormal waveform increased in amplitude (Phase 4) disappearing after 2 minutes of rest (Stage 5) During this rest period the patient received sublingual nitroglycerin Stage 6 depicts the impedance tracing taken after 6 minutes of work at 0 watts Notice the absence *of the early diastolic impedance waveform 6 minutes after nitroglycerin administration*

with *myocarditis* (R Mancini personal communication)

Case Report The patient a 15 year old male was admitted on September 9 1975 with the diagnosis of *myocarditis presumably viral* The clinical course was uneventful The initial resting impedance *tracing done on September 12* shows the abnormal early diastolic impedance waveform described in *this report* (*Fig 7*) Severe abnormality is observed in the systolic ejection wave in this initial tracing *He was treated* with diuretics and digitalis The second tracing (September 19) was taken at rest 24 hours after initiation of therapy The abnormal waveform is still present Marked improvement is observed in the systolic ejection wave The third resting tracing (September 22) was obtained after full digitalization This last one depicts further regression of the abnormal early diastolic impedance waveform along with improvement in the systolic ejection wave The patient was discharged on September 22 1975 He died suddenly two weeks after discharge

Many prognostic factors are considered by the physician at the time of admission of patients with diverse myocardial insults—their age *their* previous history clinical status on admission and the location and extent of the injury to *mention*

Myocarditis
Age 15 ♂

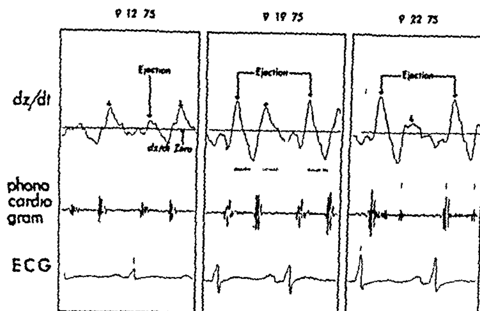


Fig 7 Resting impedance recordings obtained in a 15 year old male patient admitted with the diagnosis of myocarditis See text for explanation (Published as a courtesy and with the permission of Dr Ralph Mancini Postgraduate Medical Fellow University of Minnesota Hospitals)

a few Despite these many factors the initial assessment of the patient s prognosis in terms of his hospital course, complications reinfarction and death is not possible in most cases The non invasive technique of thoracic impedance recordings at the time of admission has offered us the identification of an abnormal impedance wave form that, in retrospective analysis, appeared in the patients who eventually developed severe complications while in the hospital The relationship between the presence of this abnormal wave form and the poor outcome as given by the New York Heart Association Functional Classification, is highly significant Its relation to the patients who eventually died is even more impressive From these data it is clear that this abnormal waveform serves to identify the patients in greater risk both in terms of complications functional outcome and even death

Summary

The first derivative of the thoracic impedance (dZ/dt) was recorded in 81 patients entering the Cardiac Care Unit with diverse acute cardiovascular illnesses An abnormal diastolic impedance waveform was identified in 30 of the patients These were compared with the other 51 patients admitted under similar circumstances who did not show this abnormal waveform Retrospective analysis of these 81 patients reveals that the ones showing the abnormal wave eventually had a poorer prognosis (66 per cent were eventually classified as Class III and IV) versus 90 per cent of the patients without the abnormality who were eventually classified under Class I and II ($\chi^2 = 28.6$ $p < .001$)

More than 50 per cent of the 30 patients who showed the abnormality died and 16 out of the 18 who died belonged to the group who showed the abnormal waveform ($\chi^2 = 26.7$ $P < .001$)

From this analysis it appears that the presence of this abnormal early diastolic waveform of the dZ/dt tracing can be used as a predictor of outcome in patients with several myocardial insults both in terms of functional disability and death

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Results of valve replacement with the Lillehei-Kaster disc prosthesis

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The choice of a prosthesis for replacement of a diseased cardiac valve is based on its mechanical efficiency low incidence of complications and ease of insertion Caged prostheses may cause significant valvar obstruction[1] and may be difficult to insert in patients with small aortic roots They may malfunction or cause arrhythmias when inserted in the mitral position in patients with small ventricular cavities

The Lillehei Kaster aortic and mitral valves were designed with the objective of eliminating these problems[2] They are low profile valves which have a pivoting disc with central flow to reduce transvalvar gradients and thrombus formation The disc tilts eccentrically with four fifths of the flow passing through the larger orifice and one fifth through the smaller The disc is made of thrombo resistant Pyrolite The titanium base and retaining struts are bare while the outer annulus is covered with knitted Teflon The reported functional and hemodynamic advantages[3] prompted us to submit these valves to critical trial in our clinic This report deals with the results of aortic and mitral valve replacement in a series of 150 patients

Subjects and methods

An unselected total of 150 patients underwent valve replacement surgery with Lillehei Kaster prostheses during the period July 1972 to December 1973 These may be grouped as follows

Aortic valve replacement 71 patients (72 operations) All these patients were symptomatic 53 were in Class III or IV (N Y Heart Association) and 12 in Class II five had embolism from previous aortic valve replacement and two had aortic insufficiency following treatment for infected prosthetic valves Infective endocarditis was present at the time of operation in five patients

Mitral valve replacement 62 patients (63 operations) Fifty nine were in Class III or IV at the time of surgery and four were in Class II

Double and triple valve replacement 17 patients All these patients were in Class III or IV

Warfarin therapy was administered postoperatively to 120 of the 137 surviving patients with the objective of controlling the Quick prothrombin time between 22 and 30 seconds In 17 patients it was withheld because distance to be travelled made it impractical specific contraindications were present or patients were unreliable Follow up extended from 18 to 40 months We examined 103 of the patients at our outpatient clinic at three monthly intervals except those living at a long distance where information was obtained by letter from these patients and their physicians Five patients were lost to follow up The results were analyzed using actuarial methods described by Anderson and co workers Only occurrence of definite embolism or valve thrombosis were included in analyses Episodes of dizziness, transient visual disturbances or emboli from infected prosthetic valves were not analyzed Cerebral

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emboli were termed major if permanent neurological deficit resulted and transient if the patient recovered completely

Results

Aortic valve replacement

Operative mortality and postoperative disability Six intra operative or hospital deaths occurred (8% mortality) Prosthetic valve malfunction was not implicated in any of these deaths Of the 65 survivors 9 patients had Class II or more disability Four of these patients had infective endocarditis at time of surgery

Late deaths Fourteen patients died after discharge from hospital two from infective endocarditis two from thromboembolism two from cardiac failure and three from non cardiac disease two had diffuse coronary artery disease incompletely revascularized with aortic coronary bypass grafts Three patients died suddenly and unexpectedly The cause of death was not evident at autopsy in two of the latter patients

Thromboembolism Six of the surviving patients (9 per cent) developed thromboembolic complications Two of these patients who were not receiving anticoagulants died one had a minor and a major cerebral embolus and the other had a thrombosed prosthetic valve (proved at postmortem) In the other four patients all receiving anticoagulants there were three transient and one major cerebral embolic episodes Actuarial analysis of deaths and thromboembolism is shown in Fig 1 The cummulative thromboembolic free rate three years following aortic valve replacement was 89 per cent

Mechanical problems No instance of mechanical malfunction of prostheses apart from thrombosis was recorded One patient with infective endocarditis at the time of surgery developed significant paravalvar leak and underwent reoperation Specific investigations to detect minor degrees of hemolysis were not undertaken but overt hemolytic anemia was not observed

Valve sounds and murmurs An opening sound was audible in only two patients It was soft and could have been easily missed Phonocardiograms were recorded in 31 patients and opening sounds were noted in five An ejection systolic murmur was recorded in 28 patients

Mitral valve replacement

Operative mortality and postoperative disability Seven operative or hospital deaths occurred

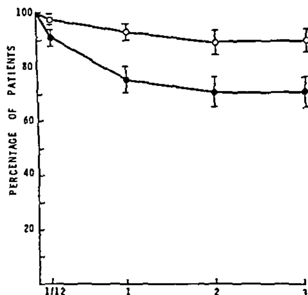


Fig 1 Actuarial survival and thromboembolic incidence in 71 patients (?? operations) given Lillehei Kaster aortic prostheses *Solid circles* = per cent survival *open circles* = per cent thromboembolic free patients *Vertical bars* denote standard errors

(11 per cent mortality rate) No deaths were attributed to prosthetic valve malfunction Eighteen of the surviving 55 patients had Grade II or more disability

Late deaths Seven late deaths occurred one from a thrombosed valve one from infective endocarditis one from intracerebral hemorrhage related to anticoagulant therapy one from non cardiac disease and three from cardiac failure (one of these had a normal prosthetic valve function at recatheterization the other two developed their symptoms acutely and were not recatheterized or examined postmortem)

Thromboembolism Seven of the surviving patients (13 per cent) all of whom received Warfarin therapy developed thromboembolic episodes One patient had a transient cerebral episode and another required a femoral embolectomy Five patients had a total of 6 episodes of valvar thrombosis with acute or subacute left heart failure Emergency valve replacement was successfully undertaken in three of these patients (one patient thrombosed two successive Lillehei Kaster mitral prostheses) The other two patients died one from valvar thrombosis which was present at postmortem the other following emergency surgery Two patients had multiple peripheral emboli prior to valve thrombosis The angiogram of a thrombosed valve with its opera

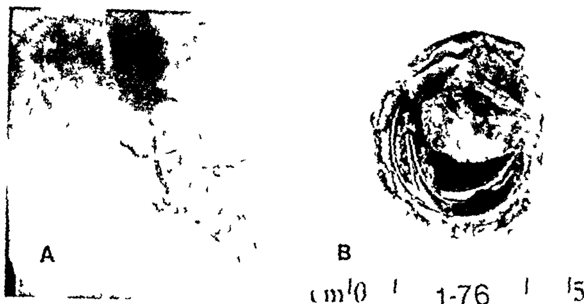


Fig 2A and B A Left ventricular angiogram in a patient with thrombosed Lillehei Kaster mitral prosthesis (R A O) The thrombus produces a translucent contrast free area on the ventricular side of the prosthesis The left atrium is filled with contrast medium due to prosthetic valvar insufficiency B The operative specimen

tive specimen is illustrated in Fig 2 In five patients the thrombus involved the bare titanium base and spread to the metal retaining struts, and occluded the smaller of the two mitral orifices Actuarial analysis of deaths and thromboembolism is shown in Fig 3 The cummulative thromboembolic free rate three years following mitral valve replacement was 78 per cent

Mechanical problems No instance of mechanical malfunction of prostheses (other than thrombosis) or overt hemolytic anemia was detected Two patients developed mitral incompetence in the early postoperative period and were reoperated upon using Starr Edwards prostheses Both these patients had extensive calcification of the mitral annulus which made suturing difficult

Valve sounds and murmurs Phonocardiograms were recorded in 34 patients postoperatively Apical mid diastolic murmurs were observed in 21 patients (62 per cent) A mitral systolic murmur was not recorded in any patient with a normally functioning prothesis A soft mitral opening sound was audible in two patients and phonocardiographically recorded in five (15 per cent)

Multiple valve replacement There were no operative deaths Four late deaths occurred two from thromboembolism one from infective endocarditis and one patient who was recatheterized postoperatively and had normal prosthetic aortic and mitral valve function died with low cardiac output Three patients (18 per cent) had thromboembolic episodes one who was not receiving anticoagulants died of a cerebral embolus one died of a thrombosed prosthesis confirmed at postmortem and one had a transient cerebral episode One patient developed severe hemolytic anemia with a hemoglobin of 7 Gm per cent corrected reticulocyte count 7 5 per cent serum bilirubin 2 5 mg per cent haptoglobin under 20 mg per cent and LDH 1324u Hemosiderin was present in the urine Following oral iron therapy this patient has maintained a normal hematocrit

Discussion

In a series of 68 patients alternately given Lillehei Kaster and Bjork Shiley disc aortic prostheses Nitter Hauge and colleagues clinically assessed the Lillehei Kaster valve to be satisfactory and no different from the Bjork Shiley prosthesis No thromboembolic episodes were recorded during a one year follow up period Lillehei and associates recorded two transient thromboembolic episodes during a two year follow up of 75 patients with aortic or mitral valve replacement In their series anticoagulant therapy was given only to patients with more advanced preoperative cardiac disease They reported there was no evidence of significant postoperative intravascular hemolysis

In the present series of 150 patients the results have been analyzed by actuarial methods The operative mortality rate which was partly due to the patients poor preoperative state was not attributed to the prosthesis itself in any instance

A serious thromboembolic rate occurred particularly in patients with mitral prostheses despite anticoagulant therapy. Patients with obstructed prostheses had extensive thrombus formation on the bare metallic base extending to the metallic struts. We believe this bare metal to be a nidus for thrombus formation and possibly a serious defect in valve design.

Only rarely were opening sounds of aortic and mitral prostheses audible or phonocardiographically recordable. This series confirms the report by Gibson and co workers of low intensity and infrequency of recorded mitral openings sounds and the frequent occurrence of mid diastolic murmurs but contrary to that report in our patients mitral systolic murmurs were not recorded with normally functioning prostheses. In our series early detection of significant mitral valve obstruction by auscultation and phonocardiography was difficult because a mid diastolic murmur and absence of an opening sound was frequently encountered in apparently normally functioning valves. Valvar obstruction was suspected when sudden left heart failure occurred.

In non thrombosed aortic and mitral prostheses in our series the hemodynamic results have been satisfactory on clinical assessment. We attributed postoperative effort intolerance and cardiac decompensation to residual cardiac disease. In a separate report to be published on the results of postoperative recatheterization of our patients we document that the mitral and larger aortic prostheses have a satisfactory calculated functional valve area whereas the smaller aortic valves produced significant valve obstruction.

No instance of prosthetic malfunction excluding valvar thrombosis was detected. One patient with an aortic and mitral prosthesis developed overt intravascular hemolysis.

Our conclusion is that Lillehei Kaster aortic and mitral valve prostheses have not been satisfactory in our series of patients. A significant thromboembolic rate has been encountered and has discouraged us from continuing to use these prostheses in our institution.

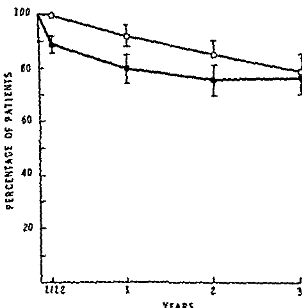


Fig 3 Actuarial survival and thromboembolic incidence in 62 patients (63 operations) given Lillehei Kaster mitral prostheses. Symbols as in Fig 1

Summary

The results of valve replacement in 150 patients with Lillehei Kaster aortic and mitral prostheses followed for 20 to 40 months are reviewed. Actuarial analysis showed 78 per cent cummulative thromboembolic free rate three years following mitral valve replacement and 89 per cent following aortic valve replacement. Five patients had a total of six episodes of mitral valve thrombosis despite anticoagulant therapy. Early detection of mitral valve obstruction was difficult because a mid diastolic murmur and absence of an opening sound was frequently encountered in normally functioning prostheses. Hemodynamic results assessed clinically in patients with non thrombosed prostheses were satisfactory.

Addendum

A recent report has indicated that rapid washout of angiographic dye in the aorta was observed only on the larger opening side of the Lillehei Kaster disc valve whereas turbulence and persistence of contrast medium with delayed washout occurred on the smaller orifice side.[a] We believe this to possibly be an explanation for our observation that the thrombus formation was always in the smaller of the two orifices of thrombosed prostheses.

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Systolic time intervals in chronic anemia

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It is well known that chronic anemia is associated with hemodynamic alterations like increased cardiac output and stroke volume and decreased peripheral vascular resistance Characteristic changes in systolic time intervals are known to accompany alterations in various hemodynamic parameters Although hemodynamic studies in chronic anemia have been reported by several investigators there is only one report of systolic time intervals in chronic anemia Systolic time intervals measured by non invasive techniques have been shown to be a convenient means of evaluation of myocardial performance We have measured systolic time intervals in patients with chronic anemia in an attempt to determine the effect of chronic anemia on the phases of cardiac systole and on left ventricular performance

Materials and methods

Four groups of subjects were studied (Table I) All were free of any clinically evident underlying cardiovascular disease Group I (Control group) consisted of 12 healthy subjects aged 17 to 40 years (mean 28 ± 7 years) having hemoglobin concentration of 12 to 15 Gm per cent (Mean 13 2 ± 1 2 Gm per cent) Groups II III and IV (total 32 cases) were patients with anemia of at least two months duration as estimated by history Anemia was due to ankylostomiasis in 15 cases post partum in 7 cases and due to varied etiology in 10 cases Group II (mild anemia) included 15 cases aged 13 to 66 years (mean 38 ± 17 years) had hemoglobin concentration ranging between 7 to 11 8 Gm per cent (mean 10 1 ± 1 3 Gm per cent) Group III (severe anemia without congestive failure) consisted of 13 cases aged 14 to 70 years (mean 37 ± 17 years) with hemoglobin ranging between 1 5 to 6 0 Gm per cent (mean 3 8 ± 1 7 Gm per cent) and Group IV (severe anemia with congestive failure) included four cases aged 22 to 60 years (mean 40 ± 18 years) with hemoglobin ranging between 1 4 to 6 0 Gm per cent (mean 4 7 ± 2 2 Gm per cent) Presence of peripheral pitting edema or hepatomegaly with jugular venous engorgement or persistent fine crepitations at lung bases with chest x ray showing cardiomegaly and pulmonary vascular congestion were considered evidences of congestive failure

Systolic time intervals were determined from simultaneous recordings of phonocardiogram electrocardiogram and carotid pulse tracings obtained with subjects supine and resting about 2 hours postprandial using a Hewlett Packard Model 1514B ECG/Phono system Phonocardiogram was recorded by a contact microphone (HP 2105 A) from an area over the precordium which allowed best visualization of the initial high frequency vibrations of the second heart sounds Carotid pulse tracing was obtained from the right carotid artery in the neck through a funnel shaped pickup attached to an air coupled pulse wave transducer (HP 21051 D) The electrocardiographic Lead I II or III (whichever showed best q waves) was recorded simultaneously The paper speed was 50 mm /sec with time markings at 20 msec The recordings were

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Table I The subjects included in the study

	Group I—Control	*Group II—Mild anemia*	*Group III—Severe anemia without congestive failure*	*Group IV—Severe anemia with congestive failure*
No of cases	12	15	13	4
Sex				
Male	11	11	6	1
Female	1	4	7	3
Age (years)				
Range	17 40	13 66	14 70	22 60
Mean ± SD	28 ± 7	38 ± 17	37 ± 17	40 ± 18
Hemoglobin (Gm %)				
Range	12 0 15 0	7 0 11 8	1 5 6 0	1 4 6 0
Mean ± SD	13 2 ± 1 2	10 1 ± 1 3	3 8 ± 1 7	4 7 ± 2 [illegible]
Cause of anemia				
Ankylostomiasis	—	7	6	2
Postpartum	—	—	5	2
Others	—	8	2	—

Table II Mean systolic time intervals in the four groups of subjects studied

	Group I (Control)	*Group II (Mild anemia)*	*Group III (Severe anemia without congestive failure)*	*Group IV (Severe anemia with congestive failure)*
Heart rate (per min)	75 ± 11	76 ± 26	88 ± 17	103 ± 15
PEPc (msec)	123 ± 9	127 ± 8	112 ± 14	141 ± 8
LVETc (msec)	413 ± 7	412 ± 12	429 ± 25	388 ± 30
QA c (msec)	536 ± 13	540 ± 14	541 ± 24	529 ± 36
PEP/LVET	0 326 ± 0 03	0 334 ± 0 04	0 270 ± 0 05	0 455 ± 0 01

made with breath held at normal end expiration and measurements were made to the nearest 10 msec Total electromechanical systole (QA) was measured from the onset of q wave to the onset of first high frequency vibrations of second heart sound left ventricular ejection time (LVET) was measured from the onset of rapid upstroke to the trough of the dicrotic notch of carotid pulse tracing and pre ejection period (PEP) was calculated by subtracting LVET from QA These measurements were corrected for heart rate by a nomogram constructed by us (Fig 1) based on the formulae of Weissler and Garrard PEP/LVET ratio was calculated from uncorrected measurements

Results

The findings of heart rate and rate corrected PEP LVET and QA (PEPc LVETc and QA c, respectively) and PEP/LVET ratio in each of the four groups of cases are summarized in Table II

The heart rate in the control group (Group I) was 75 ± 11 beats per minute (mean ± S D) In the group with mild anemia (Group II) it was 76 ± 26 beats per minute which was not significantly different from the control group In the groups of severe anemia without congestive failure (Group III) and with congestive failure (Group IV) the heart rate was significantly higher than in the control group (88 ± 17 beats per minute $P < 0\ 05$ and 103 ± 15 beats per minute $P < 0\ 001$ respectively)

The mean PEPc in Group I was 123 ± 9 msec In Group II it was 127 ± 8 msec which was not significantly different from Group I But in Group III it was 112 ± 14 msec which was significantly less ($P < 0\ 05$) and in Group IV it was 141 ± 8 msec which was significantly higher than in the control group ($P < 0\ 001$)

The mean LVETc in the control group was 413 ± 7 msec In Group II it was 412 ± 12 msec which was not significantly different from the control group but in Group III (429 ± 25 msec)

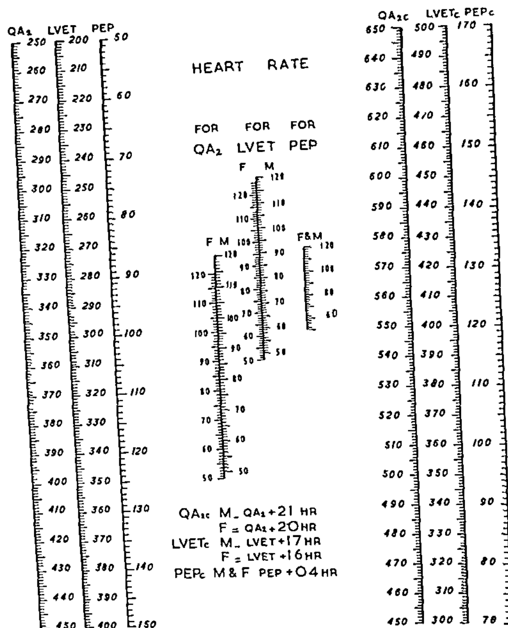


Fig 1 Nomogram for correction of observed values of systolic time intervals for heart rate based on the formulae of Weissler and Garrard To use the nomogram for correction of QA place a straight edge at the observed value of QA on the QA scale on the left side and the observed heart rate on the "heart rate for QA" scale in the middle and read the rate corrected QA on the QA c scale on the right side Similarly for correction of observed LVET use the scales labelled as LVET Heart rate for LVET and "LVETc and for correction of observed PEP use the scales PEP Heart rate for PEP and PEPc It should be noted that separate scales are provided for female and males for heart rate for QA and LVET but the same scale is to be used for both sexes for heart rate for PEP QA c may also be calculated by adding LVETc and PEPc thus providing a double check on the readings of the nomogram

it was significantly higher ($P < 0.05$) and in Group IV (388 ± 30 msec) it was significantly less than in the control group ($P < 0.001$) There was marked variation in the findings among cases in Groups III and IV as indicated by large standard deviations in these two groups

The mean QA c in the control group was 536 ± 13 msec In Group II (540 ± 14 msec) and Group III (541 ± 24 msec) it was not significantly different from the control group but in Group IV (529 ± 36 msec) it was significantly lesser than in the control group ($P < 0.01$) As in LVETc there was wide variation in QA c also among the cases in Groups III and IV

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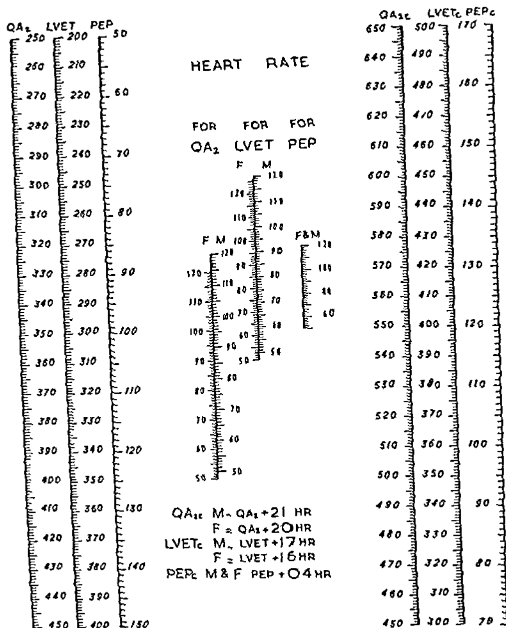


Fig. 1. Nomogram for correction of observed values of systolic time intervals for heart rate based on the formulae of Weissler and Garrard. To use the nomogram for correction of QA$_2$ place a straight edge at the observed value of QA$_2$ on the "QA$_2$" scale on the left side and the observed heart rate on the "heart rate for QA$_2$" scale in the middle and read the rate corrected QA$_2$ on the "QA$_2$c" scale on the right side. Similarly for correction of observed LVET use the scales labelled as "LVET", "Heart rate for LVET" and "LVETc" and for correction of observed PEP use the scales "PEP", "Heart rate for PEP" and "PEPc". It should be noted that separate scales are provided for females and males for heart rate for QA$_2$ and LVET but the same scale is to be used for both sexes for heart rate for PEP. QA$_2$c may also be calculated by adding LVETc and PEPc thus providing a double check on the readings of the nomogram.

it was significantly higher ($P < 0.05$) and in Group IV (388 ± 30 msec.) it was significantly less than in the control group ($P < 0.001$). There was marked variation in the findings among cases in Groups III and IV as indicated by large standard deviations in these two groups.

The mean QA$_2$c in the control group was 536 ± 13 msec. In Group II (540 ± 14 msec.) and Group III (541 ± 24 msec.) it was not significantly different from the control group but in Group IV (529 ± 36 msec.) it was significantly lesser than in the control group ($P < 0.01$). As in LVETc there was wide variation in QA$_2$c also among the cases in Groups III and IV.

The mean PEP/LVET ratio was 0.326 ± 0.03 in the control group. In Group II (0.334 ± 0.04) it was not significantly different from the control group, but in Group III (0.270 ± 0.05) it was significantly less ($P < 0.01$) and in Group IV (0.455 ± 0.01) it was significantly higher than in the control group ($P < 0.001$).

Discussion

Hemodynamic studies in resting subjects with chronic anemia by several investigators have established that there is no discernable hemodynamic abnormality in patients with mild anemia (hemoglobin above 7 Gm. per cent).[1] We found that systolic time intervals were also normal in such cases. When hemoglobin is less than 7 Gm. per cent, cardiac output is known to be increased mainly due to decreased peripheral vascular resistance causing increased speed of circulation and consequent increased venous return resulting in increased stroke volume. Investigations designed to determine the effect of alterations in stroke volume on systolic time intervals have shown that increase in stroke volume due to enhanced ventricular filling is accompanied by decrease of PEP and increase of LVET while QA remains unaltered. We found that in chronic severe anemia where cardiac output is known to be increased due to increased stroke volume, the pattern of systolic time intervals usually associated with increased stroke volume (i.e., decreased PEP, increased LVET, and decreased PEP/LVET ratio) was found only when there was no congestive failure. In our cases of severe chronic anemia with congestive failure, the pattern of systolic time intervals was just the opposite, i.e., increased PEP, decreased LVET, and increased PEP/LVET ratio. This pattern is usually found in heart failure with reduced cardiac output and stroke volume and is considered to be the result of impaired left ventricular performance. The congestive failure in chronic anemia is a high output failure, where although the cardiac output is higher than the normal, it is believed to be deficient relative to the needs of the body.[1] Thus in chronic anemia with congestive failure, where cardiac output may still be higher than normal, impairment of myocardial performance is clearly evident by the characteristic alterations of the systolic time intervals.

Manchanda and colleagues studied cases of chronic severe anemia (hemoglobin < 6.5 Gm. per cent) without congestive failure and found no change in QA or LVET but significant increase in PEP and concluded that this represented depressed myocardial contractility or subclinical left ventricular failure. But in our cases of chronic severe anemia without congestive failure (our Group III) the PEP was reduced and LVET was increased. We found increased PEP only in our cases of chronic severe anemia with congestive failure (our Group IV) who in addition also had reduced LVET.

We found wide variations in systolic time intervals in cases with severe anemia both with and without congestive failure. Although as groups these cases showed characteristic alterations, for any individual patient the systolic time intervals could not be predicted from hemoglobin levels. Such variability has been reported in hemodynamic measurements also.[4] A possible explanation for this may be that myocardial performance in these cases is determined not only by the degree of anemia but also by such other factors as the state of hydration and nutrition of the patient and the presence of subclinical cardiovascular disease.

Recently there has been great interest in the use of systolic time intervals for evaluations of left ventricular performance in many clinical situations. Our study shows that chronic anemia can cause alterations in these measurements. Therefore hemoglobin levels of the subjects must also be taken into account while interpreting systolic time intervals.

Summary

Systolic time intervals were measured noninvasively in 12 healthy control subjects (hemoglobin 12 to 15 Gm. per cent) and 32 cases of chronic anemia without underlying cardiovascular disease. It was found that in mild anemia (hemoglobin above 7 Gm. per cent) where cardiac output is known to be normal, the systolic time intervals were also normal. In severe anemia (hemoglobin below 7 Gm. per cent) where cardiac output is known to be high, the systolic time intervals showed the pattern usually associated with high cardiac output, i.e., increased left ventricular ejection time (LVET) and decreased pre-ejection period (PEP) and PEP/LVET ratio only when congestive failure was absent. In

severe anemia with congestive failure the LVET was decreased and PEP and PEP/LVET ratio were increased—the pattern associated with impaired myocardial performance even though cardiac output is known to be high in such cases also

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Variability of early lidocaine levels in patients

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Lidocaine is an effective antiarrhythmic agent usually given as a bolus and constant infusion in the treatment of ventricular arrhythmias. Both the antiarrhythmic effectiveness and toxicity have been correlated with blood or plasma levels.[1-4] Many studies indicate a minimum therapeutic whole blood level of 1.8 μg/ml.[4] Due to red blood cell partitioning and protein binding, this would be equivalent to approximately 2.4 μg/ml in plasma.

The pharmacokinetics of lidocaine in man have been described using a two compartment open model. When a bolus and constant infusion of lidocaine are computer simulated using this model, an early dip below therapeutic plasma levels is present as shown in Fig. 1. The dip begins a few minutes after the bolus and lasts up to two hours. The occurrence of this dip has also been postulated by Shen and Gibaldi but has not been demonstrated in man.

Since the antiarrhythmic effect correlates with blood levels, the existence of this dip could explain the recurrence of arrhythmias in some patients shortly after the initiation of lidocaine therapy. The present study examines the early pharmacokinetics of lidocaine after a bolus and constant infusion in normal volunteers and in patients with coronary artery disease (CAD). The results of this study confirm the predictive model in many, but not all, patients.

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Subjects

Normal volunteers included five males and one female 20 to 34 years of age without evidence of cardiac, hepatic, or renal disease. The eight patients with CAD included six males and two females who were 40 to 86 years old. The clinical features of these patients are shown in Table I. Informed consent was obtained from all participants.

Methods

The volunteers and patients were studied in the postabsorptive, resting supine position. An intravenous (IV) line was placed in each arm. One line was used for the lidocaine infusion and the other for venous sampling.

After control samples, all subjects received a 1 mg/Kg IV bolus over one minute and a 35 μg/Kg/min constant infusion delivered with a Harvard infusion pump. The constant infusion was maintained for three hours. Heparinized blood samples were collected at 2, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, and 180 minutes after lidocaine was started. The separated plasma was frozen until analyzed. Plasma lidocaine was analyzed[11] by gas liquid chromatography using a 1200 Varian Aerograph. Student's t test for unpaired values was used to assess the statistical significance of group differences.

Mathematical model. A two compartment, open model was used to predict the lidocaine levels in the plasma as a function of time after the initial dose as shown in Fig. 1. The kinetic model is shown in Fig. 2. The equations representing the

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Table I Patients with CAD

Case No	*Age (yrs)*	*Diagnosis*	*Clinical class*	*Plasma dip*
1	8[illegible]	Coronary artery disease congestive heart failure	#1 Congestive heart failure Clinical Class IV	No
2	[illegible]5	Coronary artery disease congestive heart failure	#2 Congestive heart failure Clinical Class IV	No
3	40	Unstable angina	#3 Clinical Class I	Yes
4	57	Acute M I	#4 Killip Class I	Yes
5	50	Acute M I	#5 Killip Class I	Yes
6	54	Acute M I	#6 Killip Class II	No
7	69	Acute M I	#7 Killip Class II	No
8	49	Acute M I	#8 Killip Class III	No

American H[illegible]rt Association Clinical Classificati[illegible]n

mass balance and concentrations for the model are given in equations 1 and 2 These were used to construct the curves shown in Fig 1

$$V_1\frac{dC_1}{dt} = (R + k\ V_2C\ ) - (k_{12}V\ C\ + k\ V\ C\ ) \quad (1)$$

$$V_2\frac{dC_2}{dt} = k_{12}V_1C\ - k_2\ V_2C_2 \quad (2)$$

mass accumulated = mass in − mass out

Where

V_1 V_2 are volumes (ml)
C_1 C_2 are concentrations (μg/ml)
k k k are rate constants (min)
R is rate of infusion of drug − (μg/min)

For lidocaine k represents primarily hepatic metabolism from the central compartment while k and k refer to mass transport between the two compartments The equations were solved analytically for a loading dose followed by a constant infusion and the final equations are given in equations 3 and 4 These equations were incorporated into a program on a Wang 2200C to produce the curves shown in Fig 1

$$C = \frac{k_{e1}\ ^{\beta}}{k\ (\alpha - \beta)}\ (C\ \alpha - \frac{R}{V})e + \frac{k_{e1} - \alpha}{k\ (\beta - \alpha)}\ (C\ ^{\beta} - \frac{R}{V})e^{\beta} + \frac{R}{V\ k_e} \quad (3)$$

$$C = \frac{V}{V}\ \frac{k}{\alpha(\beta - \alpha)}\ (C\ \alpha - \frac{P}{V})e + \frac{V}{V}\ \frac{k_{12}}{\beta(\alpha - \beta)}\ (C\ ^{\beta} - \frac{R}{V})e^{\beta} + \frac{k_2 R}{V_2\ \alpha\ \beta} \quad (4)$$

The nomenclature is the same as before although the following substitutions for terms have been made

$$\alpha + \beta = k_{12} + k\ + k$$

$$\alpha\ \beta = k_{21}k$$

$$\alpha = \frac{(k_{12} + k\ + k\ ) + [(k\ + k_{21} + k_{e1}) - 4k_{21}k\ ]}{2}$$

$$\beta = \frac{(k\ + k_{21} + k_{e1}) - [(k_{12} + k\ + k\ )^2 - 4k_{21}k_{e1}]}{2}$$

The expression α is the rate constant for the initial rapid phase following an intravenous injection and β is the rate constant for the slower phase of elimination[1] The value of V_2 is difficult to obtain and actually represents an average effective volume of a heterogeneous group of tissues which includes the cardiac receptor[1] Therefore the value C_2 V_2 the mass of drug in compartment 2 was used in calculations involving the second compartment

Results

Fig 3 shows the concentration time curve obtained for all 14 patients The lidocaine plasma levels are expressed as the mean plus one standard deviation After an initial value 4 48 ± 2 65 μg/ml at 2 minutes a dip below the therapeutic plasma levels occurs *This dip persists for approximately 90 minutes*

The two groups were then examined separately *The results* of this comparison are shown in Fig 4 In normal volunteers the two minute plasma level was 2.97 ± 2 0 μg/ml and fell rapidly below therapeutic levels resulting in a dip which persisted for more than 90 *minutes In* the group of patients with CAD the two minute mean plasma level 5 53 ± 2.35 μg/ml was significantly ($p < 0\ 05$) higher than normal volunteers After two minutes the lidocaine levels fell in the CAD

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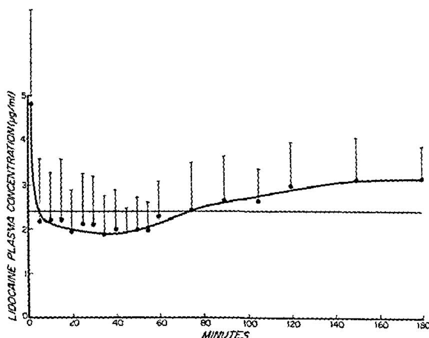


Fig 3 The concentration time curve for all subjects with lidocaine concentration expressed as the mean ± 1 S D The horizontal line represents minimal therapeutic plasma levels of 2.4 µg/ml

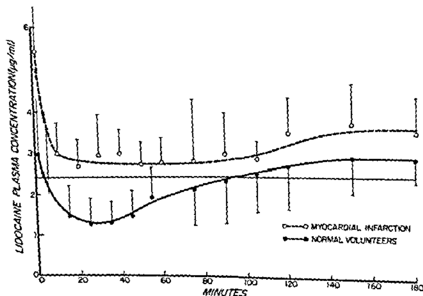


Fig 4 The lidocaine concentration time curves for patients with CAD and normal volunteers

may explain the recurrence of arrhythmias in some patients shortly after the initiation of lidocaine therapy Patients with CAD and minimal hemodynamic compromise could be anticipated to have a more pronounced plasma dip This is further supported by examination of Table I which shows the dip occurring only in patients who are in Clinical or Killip Class I The difference in ages between both groups probably did not affect our results since no differences in the disposition kinetics of lidocaine between young and older normal subjects has been found

To avoid or attenuate this dip several approaches can be offered (1) The bolus dose could be increased as shown in Fig 1 but this may increase the risk of acute toxicity Prolongation of

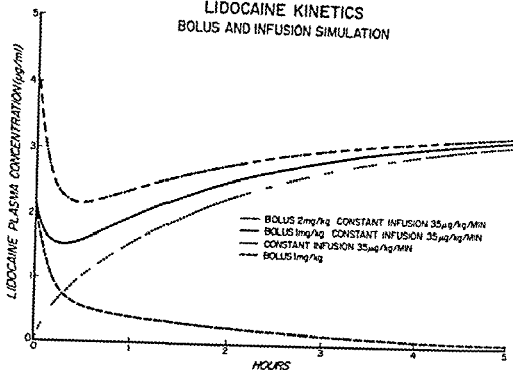


Fig 1 Computer simulated plasma lidocaine concentrations using previously published kinetic parameters The upper two curves demonstrate the dip resulting from different bolus doses and the same constant infusion

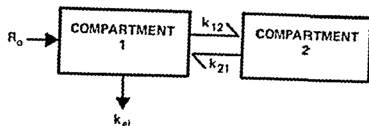


Fig 2 The two compartment open model used to describe lidocaine kinetics See text for discussion

group but not below the minimum therapeutic concentration of 2 4 μg/ml (Fig 4) The differences between normal volunteers and CAD patients were significant ($p < 0\,0125$ to $p < 0\,005$) from ten minutes through 60 minutes The separation of normal volunteers and CAD patients however did not completely separate those with from those without plasma lidocaine dips The patients with an acute myocardial infarction in Clinical Class I and a patient with unstable angina (Table I) demonstrated a significant dip below therapeutic levels shortly after starting the bolus and constant infusion An example of this is shown in Fig 5

Discussion

The results of this study show that as a group those patients with myocardial infarction had a significantly higher lidocaine level than normal volunteers at two minutes After this two minute value a dip in lidocaine levels occurs seeming to confirm the mathematical model used to describe the early pharmacokinetics of lidocaine in many but not all of the patients The dip is significantly more pronounced in normal volunteers than in patients with acute MI The latter group likely had more hemodynamic compromise particularly of hepatic blood flow Previous studies[11] have demonstrated that lidocaine has a very high hepatic extraction ratio and its clearance from plasma is dependent on hepatic blood flow Therefore lidocaine clearance will vary directly with the hepatic blood flow Patients with decreased hepatic blood flow would be expected to have reduced lidocaine clearance and therefore a smaller plasma dip than seen in normals

A decreased hepatic elimination rate of lidocaine may not be the only mechanism to explain the attenuated dip in some patients Thomson and associates[1] found a reduced volume of lidocaine distribution in patients with congestive heart failure A reduction in the volume of distribution would also tend to attenuate the plasma dip The higher lidocaine levels from two to sixty minutes in those patients with myocardial infarction and congestive heart failure emphasize the need to reduce the bolus dose as well as the constant infusion

The early dip in lidocaine plasma levels (Fig 5)

Effect of tachycardia on atrial transport in mitral stenosis*

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The physiologic role of the atrium has been defined in terms of (1) active atrial transport or booster pump function (2) passive atrial transport or conduit function and (3) the reservoir function In patients with mitral stenosis the hemodynamic significance of atrial systole has been the subject of considerable investigation Attention has been directed particularly toward the role of the atrium as a booster pump which enhances ventricular filling The purpose of this study is to quantitate separately the hemodynamic significance of active atrial transport compared with passive atrial transport of the atrium at two different heart rates in patients with mitral stenosis The use of sequential atrioventricular pacing permitted study of the hemodynamic effect of active atrial transport compared to an ineffective or absent atrial systole at two different heart rates The concomitant effect of these interventions on intracardiac hemodynamics was recorded and the resultant effect on diastolic flow across the mitral valve and integrated cardiac output was calculated

Methods and materials

After giving informed consent seven patients in sinus rhythm with mitral stenosis were studied as part of a routine transseptal and retrograde left heart catheterization The patient profile and baseline hemodynamic information is shown in Table I Demerol (Meperidine 50 to 75 mg) and Phenergan (Promethazine Hydrochloride 25 mg) were administered intramuscularly as premedication Xylocaine (Lidocaine) was used as local anesthesia for percutaneous catheterization or exposure of vessels All pressures were recorded with equisensitive P 23 Db Statham transducers* with zero pressure defined 5 cm below the angle of Louis Left ventricular pressure was recorded through a polyethylene catheter (PE 90 0 023 I D)† threaded through the Ross catheter into the left ventricle or by retrograde arterial catheterization A 15 cm polyethylene catheter (PE 160 0 015 I D)† was introduced percutaneously into the left brachial artery to monitor arterial pressure and to sample blood The external carotid pulse contour was recorded over the point of the maximal pulsation of the carotid vessel using a funnel shaped pickup connected with a P 23 Db transducer Left ventricular ejection time was determined using the method of Weissler and colleagues A No 5 or 6 bipolar pacing catheter was placed into the apex of the right ventricle through a right anticubital venotomy A No 6 Zucker pacing catheter‡ was utilized for atrial pacing Lead II of the electrocardiogram was obtained All data were recorded at a paper speed of 100 mm /sec with 20 msec time markers using a multichannel photorecorder §

Prior to instituting the experimental protocol the mitral valve gradient was measured using equisensitive gauges The mean mitral valve gradient was obtained by planimetry of ten consecutive complexes Cardiac output was deter

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‡Un ted States C thete and Instrument Corp Gl n Falls, N Y
§Electron cs f Med cine White Plains, N Y

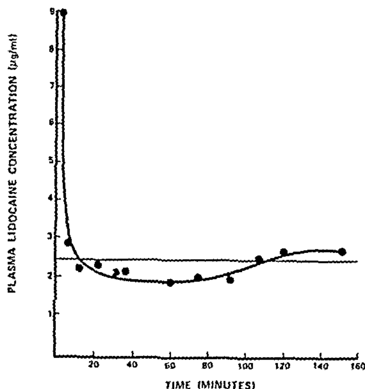


Fig 5 The lidocaine concentration time curve in one patient with acute myocardial infarction

the bolus infusion over several minutes would probably reduce this risk [1] (2) The combination of intravenous and intramuscular injections is an interesting alternative that has not been evaluated clinically However enzyme elevation from the intramuscular injection may confuse the diagnosis of myocardial infarction in certain cases (3) An exponential infusion or the method proposed by Wagner[18] for drugs with kinetics similar to lidocaine should reduce the dip but are difficult to employ clinically (4) The most practical approach at this time is probably an awareness of the potential for a dip and possible arrhythmia recurrence treated by an additional small bolus of lidocaine

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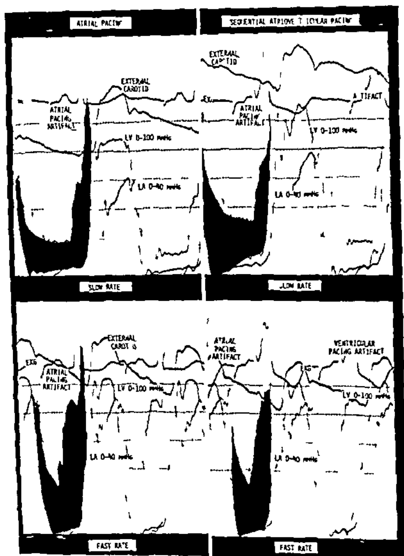


Fig. 1. Atrial pacing *(left panel)* and sequential atrioventricular pacing *(right panel)* are shown at both the slow and fast heart rate in a patient with mitral stenosis. The mitral valve gradient *(solid area)* is shown at a scale of 40 mm Hg. The left ventricular pressure is shown at a full scale of 100 mm Hg. The left ventricular ejection time is measured from the external carotid pulse tracing. Both atrial pacing and sequential atrioventricular pacing maintain a large presystolic A wave which contributed significantly to the mean mitral valve diastolic gradient. See *Fig.* 3 for statistical analysis regarding these interventions.

In each patient during each pacing state a minimum of five cycles were analyzed for (1) PR interval, (2) diastolic filling period, and (3) mean valvular gradient. In State 3 the hemodynamics associated with an absent atrial systole were compared to the two complexes immediately preceding the dropped atrial systole. A minimum of five such sequences were analyzed in each patient. Five consecutive cycles obtained during State 4 were compared with five consecutive cycles obtained during State 2 which was designated as the control period.

In two patients duplicate indicator dilution cardiac outputs were obtained during State 1, State 2, and State 4. These additional measurements of cardiac output were made in order to validate the assumption that one could estimate the integrated cardiac output on the basis of the observed diastolic mitral gradient. Cardiac outputs were done under steady state conditions during State 1 and State 2. The measurement of cardiac output during acute withdrawal of atrial systole in State 4 was done within 15 sec. of the establishment of this state so that the influence of

Table I Patient population

Patient	Age	Sex	Cardiac index (L/min)	RV pressure resting (mm Hg)	Mean mitral diastolic gradient (mm Hg)	Calculated mitral valve area (cm.)
1	25	M	2.48	32/8	6	1.[illegible]
2	25	M	2.50	35/4	6	1.7
3	4[illegible]	F	2.74	45/0	13.2	1.6
4	38	F	2.31	40/6	12	1.1
5	37	F	1.87	30/4	9	1.0
6	36	F	1.55	80/2	14	0.7
7	41	F	1.35	32/4	11	0.5

mined using either the Fick method[a] or the indicator dilution technique The method of Gorlin and Gorlin was used to calculate the mitral valve area

A series of four pacing states at two different rates was then established in each patient using a Medtronic Model No 5837 pulse generator * This instrument can be used to control both the pacing rate and the time sequence between atrial and ventricular stimulation The mitral valve gradient, left ventricular pressure left atrial pressure, and left ventricular ejection time were recorded simultaneously for each contraction throughout the subsequent interventions

State 1 was designated as atrial pacing (AP) During this intervention atrial pacing was carried out at a rate approximately 10 and 40 beats per minute faster than the patient s base line rate Ventricular activation occurred as a result of propagation of the atrial impulse through the normal cardiac conduction pathways The intrinsic physiologic delay at the atrioventricular node determined the interval between atrial and ventricular contraction Overdrive atrial pacing was utilized in order to permit the heart rate to be constant throughout all subsequent pacing interventions thus eliminating any compensatory escape rhythms which might alter the RR interval

State 2 was designated as sequential atrioventricular pacing (SEQ) This was produced by instituting sequential atrioventricular pacing with a time delay between atrial and ventricular stimulus which was less than the patient s own atrioventricular delay The right ventricle was thus activated by an ectopic pacing stimulus delivered by the right ventricular bipolar pacing catheter which arrived earlier than the stimulus initiated by atrial pacing The atrioventricular pacing delay was determined by the longest PR interval obtainable which still resulted in an ectopic QRS configuration State 2 (SEQ) was used as the control state to compare the two subsequent interventions during which atrial booster pump action was withdrawn In addition comparison of the baseline information obtained during atrial pacing in State 1 with that obtained during sequential pacing in State 2 provided evidence to show that ectopic activation of the ventricle alone in the presence of active atrial transport resulted in insignificant changes in the hemodynamic parameters observed

State 3 was designated as interrupted atrial pacing (IAP) During this intervention atrial pacing was intermittently interrupted which resulted in prolongation of atrial diastole because of overdrive suppression of the sinoatrial node The RR interval was maintained however since this intervention did not effect the ventricular pacing rate Because the atrium remained asystolic throughout the particular cycle State 3 could be used to study the acute loss of mechanical atrial systole on the subsequent ventricular systole

State 4 was designated as synchronous atrioventricular pacing (SYN) This pacing intervention was produced by simultaneously pacing the atrium and the ventricle In this circumstance atrial contraction no longer preceded ventricular contraction thus eliminating the booster pump potential of the atrium in a manner somewhat different from that utilized in State 3 State 4 was designed to study the effect of the loss of atrial transport for a brief series of contractions This could not be accomplished for more than an isolated beat in State 3

*Medtronic Inc Minneapolis, Minn

Table II continued

Patient No	Intervention	Heart Rate Slow	Heart Rate Fast	PR Slow	PR Fast	Diastolic Flow/Beat Slow	Diastolic Flow/Beat Fast	Gradient Slow	Gradient Fast	Calculated CO Slow	Calculated CO Fast	Measured CO Slow	Measured CO Fast	LVET Slow	LVET Fast
Group Means	Atrial pacing	81	110	21	23	45 3	33 6	11 2	17 5	3 7	3 4	–	–	265	298
	Sequential pacing*	81	110			44 7	32 8	12 0	15 1	3 7	3 6	–	–	260	222
	Sequential pacing	81	110	14	15	44 7	31 0	11 3	16 6	3 7	3 4	–	–	261	222
	Interrupted A V pacing	81	110	–	–	35 9	23	7 0	9 8	3 0	2 7	–	–	227	196
	Sequential pacing	81	110	13	14	45 4	32 8	12 0	16 7	3 7	3 6	–	–	260	222
	Synchronous pacing	81	110	0	0	35 4	27 6	6 9	9 7	3 0	3 2	–	–	234	205
Statistical analysis	Atrial pacing vs Sequential pacing*					>0 5	>0 5	>0 2	>0 2	>0 5	>0 2	–	–	>0 1	>0 1
	Sequential pacing vs. Interrupted A V pacing					< 001	< 001	< 001	< 001	< 001	< 05	–	–	< 001	< 005
	Sequential pacing vs Synchronous pacing					< 001	< 005	< 001	< 001	< 005	< 005	–	–	< 005	< 001
	Sequential pacing – Interrupted A V pacing vs Sequential pacing –Synchronous pacing					> 5	>0 05	>0 2	>0 5	<0 5	<0 05	–	–	< 05	< 005
	Atrial pacing (slow) vs Atrial pacing (fast)						< 001		< 001	>0 2		–	–	<0 025	

control rate Differences in the various parameters were compared by the method of paired difference

Results

Representative hemodynamic recordings showing atrial pacing (State 1 AP) sequential atrioventricular pacing (State 2 SEQ) interrupted atrial pacing (State 3 IAP) and synchronous atrial pacing (SYN State 4) at both the slower and the faster heart rates are illustrated in Figs 1 and 4 Table II shows the experimental data obtained in all patients

Fig 1 is a composite illustration demonstrating the hemodynamic information obtained during atrial pacing (State 1 AP) and sequential atrioventricular pacing (State 2 SEQ) at the slower and the faster heart rates Comparison of State 1 and State 2 can be used to evaluate the effect of ectopic ventricular stimulation in the presence of effective atrial transport Figs 2 and 3 show a comparison of the group means at both heart rates for the various parameters Increasing the heart rate alone by atrial pacing (Fig 2) is shown to result in a significant increase in mean left atrial pressure and mean mitral valve gradient as a result of the shortened diastolic filling period The cardiac output remains unchanged at both heart rates The diastolic flow per beat and the left ventricular ejection time are significantly decreased The introduction of an ectopic ventricular stimulus resulted in minimal changes in these hemodynamic values (Fig 3)

Sequential atrioventricular pacing preserves atrial booster pump function The change to interrupted atrial pacing (State 3 IAP) or synchronous atrial pacing (State 4 SYN) at both the slow and fast heart rate results in the abrupt loss of atrial transport function as is shown in Fig 4 There is an associated fall in the mitral valve gradient calculated diastolic flow across the mitral valve calculated cardiac output and left ventricular ejection time The group mean results comparing sequential atrioventricular pacing and interrupted atrial pacing at both heart rates are shown in Fig 5 The group mean results comparing sequential atrioventricular pacing and synchronous atrioventricular pacing at both heart rates are shown in Fig 6 There is no statistical difference between the results obtained using either interrupted atrial pacing or synchronous atrioventricular pacing to eliminate effective atrial transport function except for interrupted atrial pacing which causes a greater

Table II Experimental data—all patients

Patient No	Intervention	Heart Rate		PR*		Diastolic Flow/Beat		Gradient		Calculated CO		Measured CO		LVET	
		Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast
1	Atrial pacing	85	114	0 16	0 18	59 2	49 7	10 6	18 9	5 0	5 7	4 5	4 6	281	23[illegible]
	Sequential pacing'	85	114	0 10	11	54 6	34 1	9 4	10 4	4 6	3 9	4 2	3 9	[illegible]	[illegible]
	Interrupted A V pacing	85	114	–	–	45 8	28 9	6 1	7 9	3 9	3 3	3 6	3 7	240	[illegible]
	Sequential pacing'	85	114	10	10	54 6	35 4	10 8	11 3	4 6	4 0	4 2	3 9	230	22[illegible]
	Synchronous pacing	85	114	0	0	40 0	32 4	6 5	7 7	3 4	3 7	3 6	3 7	25[illegible]	210
2	Atrial pacing	90	–	0 18	20	65 9	44 6	14 6	16 7	5 9	5 1			245	[illegible]
	Sequential pacing	90	–	0 14	–	60 2	–	12 7	–	5 4	–			242	–
	Interrupted A V pacing	90	–	0	–	52 9	–	8 2	–	1 8	–			213	–
	Sequential pacing	90	114	14	0 20	62 4	45 0	13 5	18 7	5 6	5 1			248	230
	Synchronous pacing	90	114	0	0	54 9	41 1	8 2	10 2	4 9	4 7			228	215
3	Atrial pacing	85	103	25	29	46 7	38 5	9 1	13 3	4 0	4 0			25[illegible]	23[illegible]
	Sequential pacing	85	103	14	15	49 6	40 9	8 8	13 0	4 2	4 2			251	[illegible]
	Interrupted A V pacing	85	103	–	–	31 9	26 7	3 8	5 6	2 7	2 7			270	195
	Sequential pacing'	85	103	15	17	47 6	39 4	7 9	13 3	4 0	4 1			241	233
	Synchronous pacing	85	103	0	0	35 8	31 2	3 3	4 7	3 0	3 2			226	210
4	Atrial pacing	76	107	25	28	38 4	31 4	9 5	17 8	2 9	3 4	4 6	4 4	–	–
	Sequential pacing'	76	107	14	15	42 9	30 6	10 6	16 6	3 3	3 3	–	–	–	–
	Interrupted A V pacing	76	107	–	–	39 3	25 8	8 4	11 9	3 0	2 8	–	–	–	–
	Sequential pacing	76	107	0 06	0 06	40 4	31 4	9 2	14 4	3 1	3 3	3 3	–	–	–
	Synchronous pacing	76	107	–	–	–	30 5	–	13 6	–	3 2	–	3 3	–	–
5	Atrial pacing	79	107	23	24	48 5	31 3	15 9	20 8	3 8	3 3	–	–	244	242
	Sequential pacing	79	107	17	18	47 6	31 6	14 2	19 0	3 8	3 4	–	–	269	[illegible]
	Interrupted A V pacing	79	107	–	–	34 9	23 1	7 3	9 5	2 8	2 5	–	–	237	248
	Sequential pacing	79	107	17	18	49 4	29 3	15 7	18 6	3 9	3 1	–	–	2[illegible]0	23[illegible]
	Synchronous pacing	79	107	0	0	34 6	25 1	7 3	10 5	2 7	2 7	–	–	238	219
6	Atrial pacing	80	109	18	21	37 3	25 5	16 8	21 2	3 0	2 8	3 4	4 0	–	–
	Sequential pacing	80	109	15	14	36 9	34 4	16 0	26 0	2 9	3 7	3 4	4 0	–	–
	Interrupted A V pacing	80	109	–	–	30 4	25 5	10 8	17 8	2 4	2 8	2 6	2 7	–	–
	Sequential pacing	80	109	15	14	36 9	34 4	16 0	26 0	2 9	3 7	3 4	4 0	–	–
	Synchronous pacing	80	109	0	0	31 2	24 0	11 9	16 9	[illegible]5	2 6	2 6	2 6	–	–
7	Atrial pacing	71	118	21	24	21 0	14 2	7 3	14 0	1 5	1 7	–	–	269	200
	Sequential pacing	71	118	14	14	21 3	14 2	7 6	14 7	1 5	1 7	–	–	270	18
	Interrupted A V pacing	71	118	–	–	16 2	9 1	4 3	6 1	1 1	1 1	–	–	273	168
	Sequential pacing	71	118	14	14	21 3	14 3	7 8	14 5	1 5	1 7	–	–	261	188
	Synchronous pacing	71	118	0	0	15 8	8 8	4 2	4 4	1 1	1 0	–	–	270	173

Abbreviations and symbols PR P R interval of the electrocardiogram in seconds DF/beat diastolic flow across the mitral valve in m[illegible] beat Gradient mean mitral valve gradient in mm Hg calculated C O cardiac output calculated using the transposed formula of Gorlin and Gorlin in liters/min measured C O cardiac output measured using indocyanine green dye in liters/min LVET left ventricular ejection time in msec

Sequential pace represents the values used for comparison with atrial pacing

Sequential pace represents the values used for comparison with interrupted atrial pacing

Sequential pace represents the values used for comparison with synchronous pacing

(Seq 1 IAP) vs (Seq 2 Syn) represents statistical analysis of the magnitude of change resulting from th[illegible] intervention of interrupted atrial pacing during sequential pacing (Seq 1 IAP) compared with the change resulting from the intervention of synchronous atrioventricular pacing during sequential pacing (Seq 2 Syn) When the method of paired differences was used to compare the calculated and measured indicator dilution cardiac outputs the P value was greater than 0 2

compensatory homeostatic mechanisms could be minimized

Diastolic flow across the mitral valve on a beat to beat basis was calculated This was done by transposing the formula of Gorlin and Gorlin and assuming that the stenotic mitral valve represented a fixed orifice obstruction using the technique described by Heidenreich and associates[4] The observations outlined were made in each patient at two different heart rates (1) the initial control heart rate which was equal to a rate 10 beats above the resting level and (2) the electrically induced tachycardia which was approximately 30 beats per minute above the initial

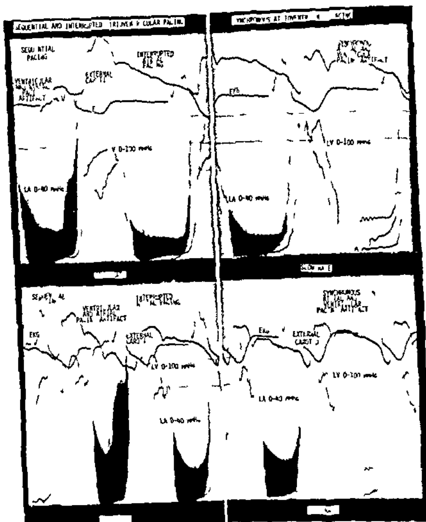


Fig 4 Sequential atrioventricular pacing and interrupted atrial pacing are shown in the *left hand panel* in a patient with mitral stenosis at both the slow and *fast heart rate* *In the right hand panel* synchronous atrioventricular pacing is shown in the same patient at both heart rates The mitral valve diastolic gradient *(solid)* is shown at a full scale of 40 mm Hg The left ventricular pressure is shown at a full scale of 100 mm Hg The left ventricular ejection time is measured from the carotid *pulse tracing* Abrupt interruption of atrial pacing *(left hand panel)* results in a loss of the presystolic contribution of effective atrial contraction to the mitral diastolic gradient as does the institution of synchronous atrioventricular pacing *shown in the right hand panel* There is a concomitant decrease in diastolic flow/beat and a reduction in the peak left ventricular systolic pressure and left ventricular ejection time during the following ventricular *contraction* when effective atrial transport is abruptly withdrawn See *Figs 5 and 6* for statistical analysis regarding these interventions

able information pertaining to the effect that sinus tachycardia has on atrial transport function in patients with mitral stenosis *Furthermore* no experimental data was available which quantitated the hemodynamic significance *of active* atrial transport as compared to passive atrial transport in patients with mitral stenosis at two different heart rates

The effect of pacemaker *induced tachycardia* in patients with mitral stenosis resulted in changes in the hemodynamic parameters which would be expected to occur as a result of an increased heart—i e there was a decrease in diastolic flow per beat stroke volume and left ventricular ejection time The cardiac output remained unchanged at both heart rates An increase in the mitral valve gradient of fifty per cent was required in order to maintain a constant cardiac output in the presence of a shortened diastolic filling period as a result of the tachycardia Similar findings have been *reported* by Nakhjavan and associates[6]

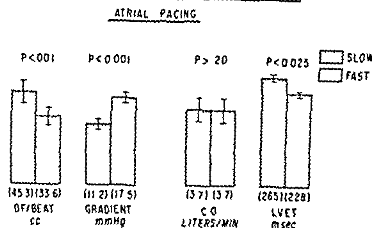


Fig 2 Comparison of the effect of increasing heart rate by atrial pacing from 81 to 110 beats per minute Group mean values and standard errors of the mean are shown for diastolic flow (DF)/beat mitral valve gradient calculated cardiac output (CO) and left ventricular ejection time (LVET) No change in cardiac output is noted The changes in the other parameters are directly attributable to the increased heart rate

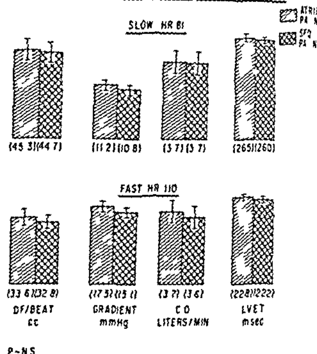


Fig 3 Comparison of atrial pacing and sequential atrioventricular pacing using the method of paired differences Group mean values and standard error of the mean are shown See Fig 2 for the legend No significant changes in these parameters result from the introduction of an ectopic ventricular pacing stimulus while effective left atrial transport is maintained

decrease in left ventricular ejection time than does synchronous atrioventricular pacing The physiologic significance of this observation, if any is not known

In Fig 7 a comparison of the magnitude of the effect which active atrial transport has on the measured parameters at two different heart rates is made The combined group data (i e pooling of the data obtained for sequential vs interrupted atrial pacing and sequential vs synchronous pacing) indicates that there is a statistically significant difference between the absolute change in mitral valve gradient diastolic flow per beat and left ventricular ejection time associated with the loss of atrial transport when the effect of abrupt withdrawal of atrial transport at the slower heart rate is compared with that of the faster heart rate The absolute contribution of effective atrial transport to mean mitral valve gradient is greater at the faster heart rate than at the slower heart rate while the absolute augmentation of diastolic flow per beat and prolongation of the left ventricular ejection time produced by effective atrial transport is reduced (Fig 2) However the per cent augmentation of mitral valve gradient diastolic flow per beat and left ventricular ejection time produced by effective atrial contraction is shown to be similar at both heart rates for the group as a whole

It should be noted that two of the seven patients have calculated mitral valve areas of less than 1 0 cm When the data from these patients (No 6 and No 7) (Table II) are analyzed separately it is evident that effective atrial transport makes an equal or greater absolute contribution to mitral diastolic flow at the faster heart rate compared to the slower heart rate Because of the decreased total diastolic flow at the faster heart rate, however effective atrial transport makes a larger percentage contribution to mitral diastolic flow at the faster heart rate

In two patients the calculated cardiac output was compared with simultaneous duplicate indicator dilution cardiogreen dye cardiac outputs There was no statistical difference between the cardiac output calculated on the basis of observed mitral valve gradient and the cardiac output as determined using the indicator dilution cardiogreen dye output technique ($P > 0 2$)

Discussion

Recently a number of studies have been performed during diagnostic cardiac catheterization in order to document the contribution that a well timed atrial contraction makes to ventricular performance in the presence and absence of valvular heart disease [9 11] The results of these studies have validated observations made in experimental animals [1 11] Until the present study was undertaken however, there was little avail

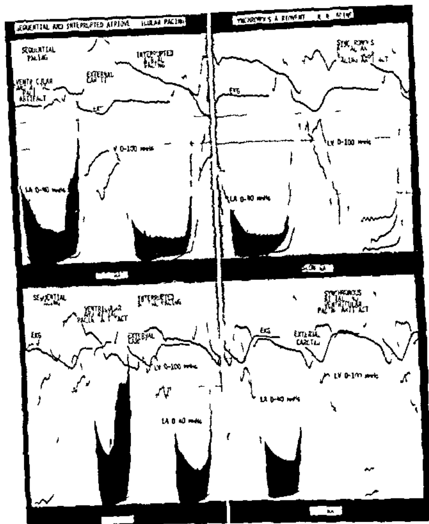


Fig. 4. Sequential atrioventricular pacing and *interrupted* atrial pacing are shown in the *left hand panel* in a patient with mitral stenosis at both the slow and fast heart rate. In the *right hand panel* synchronous atrioventricular pacing is shown in the same patient *at both heart* rates. The mitral valve diastolic gradient *(solid)* is shown at a full scale of 40 mm Hg. The left ventricular pressure is shown at a full scale of 100 mm Hg. The left ventricular ejection time is measured from the carotid pulse tracing. Abrupt interruption of atrial pacing *(left hand panel)* results in a loss of the presystolic contribution of effective atrial contraction to the mitral diastolic gradient as does the institution of synchronous atrioventricular pacing shown in the *right hand panel*. There is a concomitant decrease in diastolic *flow/beat* and a reduction in the peak left ventricular systolic pressure and left ventricular ejection time during the following ventricular contraction when *effective* atrial transport is abruptly withdrawn. See *Figs. 5 and 6* for statistical analysis regarding these interventions.

able information pertaining to the effect that sinus tachycardia has on atrial transport function in patients with mitral stenosis. Furthermore no experimental data was available which quantitated the hemodynamic significance of active atrial transport as compared to passive atrial transport in patients with mitral stenosis at two different heart rates.

The effect of pacemaker induced tachycardia in patients with mitral stenosis resulted in changes in the hemodynamic parameters which would be expected to occur as a result of an increased heart—i.e., there was a decrease in diastolic flow per beat, stroke volume, and left ventricular ejection time. The cardiac output remained unchanged at both heart rates. An increase in the mitral valve gradient of fifty per cent was required in order to maintain a constant cardiac output in the presence of a shortened diastolic filling period as a result of the tachycardia. Similar findings have been reported by Nakhjavan and associates.

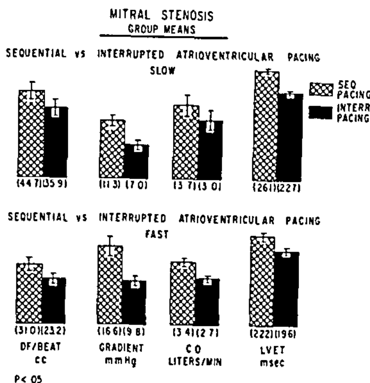


Fig 5 Comparison of the magnitude of the change resulting from the intervention of interrupted atrial pacing (IAP) during sequential (SEQ) pacing at heart rates of 81 and 110 beats/min In all instances statistically significant changes are noted in the measured parameters See *Fig 2* for the legend and *Fig 4* for the hemodynamic recordings

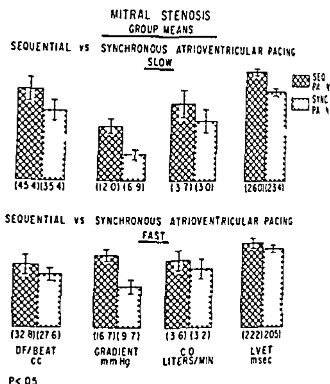


Fig 6 Comparison of the magnitude of the change resulting from the intervention of synchronous atrioventricular pacing (SYNC) during sequential (SEQ) pacing at heart rates of 81 and 110 beats/min In all instances statistically significant changes are noted in the measured parameters See *Fig 2* for the legend and *Fig 4* for the hemodynamic recordings

Quantitation of the hemodynamic significance of effective atrial transport at two different heart rates was made possible by the use of sequential atrioventricular pacing This experimental technique allowed the hemodynamic effect of active atrial transport to be withdrawn acutely so that the results of such an intervention could be studied in the absence of compensatory homeostatic mechanisms The use of right ventricular pacing resulted in only minor changes in the parameters of left ventricular function as has been shown in this and previous studies[4] The heart rate was controlled using this technique and cardiac cycles were produced which were associated with active as well as passive atrial transport activity In this manner, the contribution of active atrial transport to cardiac function was compared to the passive atrial transport function in patients with mitral stenosis

Active atrial transport increased the diastolic flow per beat mitral diastolic gradient cardiac output and left ventricular ejection time at both heart rates As shown in Fig 7, however there was a statistically significant difference between the absolute change in mitral valve gradient diastolic flow per beat and left ventricular ejection time attributable to active atrial transport at the two heart rates The absolute contribution of effective atrial transport to mean mitral valve gradient was greater at the faster heart rate compared to the slower rate, while the absolute augmentation of diastolic flow per beat and prolongation of left ventricular ejection time was reduced at the faster rate

The contribution of active atrial transport to mitral diastolic flow can be evaluated by using the Gorlin formula[8] Since flow across the stenotic valve is proportional to the square root of the mean mitral valve diastolic gradient and the mitral valve area the atrial contribution to the mean mitral valve gradient does not augment flow across the severely stenotic mitral valve as much as it would in a less stenotic valve Likewise, during tachycardia augmentation of the mitral valve gradient by active atrial transport does not increase flow across the stenotic valve as much as a similar increase in mitral valve gradient would at a slower heart rate Nevertheless effective atrial transport can be demonstrated to augment diastolic flow across the stenotic mitral valve regardless of the severity of the stenosis In patients with mild to moderate mitral stenosis (mitral valve areas greater than 1 0 cm) the contribution of active atrial trans

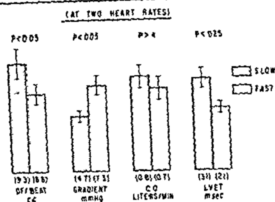
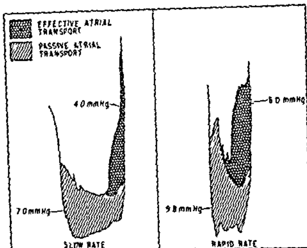


Fig 7 Comparison of the magnitude of the change resulting from abrupt withdrawal of effective atrial transport (pooling the results obtained using both interrupted atrial pacing and synchronous atrial pacing) at heart rates of 81 and 110 beats/min See *Fig 2* for the legend Effective atrial contraction increases mitral valve gradient more at the faster rate while there are smaller decreases in diastolic flow/beat and left ventricular ejection time There is no significant difference between the decrements noted in integrated cardiac output when effective atrial transport is withdrawn See text for discussion



WITHDRAWAL OF ACTIVE ATRIAL TRANSPORT

DF/BEAT cc	GRADIENT mmHg	C O LITERS/MIN	LVET msec	DF/BEAT cc	GRADIENT mmHg	C O LITERS/MIN	LVET msec
↓22%	↓38%	↓20%	↓13%	↓24%	↓40%	↓24%	↓13%

Fig 8 A graphic summary of the results of this study are shown in this illustration The mean left atrial pressure at the lower heart rate is 11 mm Hg and at the faster heart rate 15 8 mm Hg The mean mitral valve gradient increases by 50 per cent in order to maintain the cardiac output constant at the faster heart rate The mitral valve gradient is comprised of two components (1) the contribution of active atrial transport which increases from 4 to 6 mm Hg and (2) the contribution of passive atrial transport which increases from 7 to 9 8 mm Hg as the heart rate increases Effective atrial contraction augments the mitral valve gradient by 40 per cent at both heart rates Withdrawal of effective atrial contraction reduced diastolic flow/beat and integrated cardiac output by 20 per cent There is a concomitant reduction in left ventricular ejection time of 13 per cent

port to ventricular filling is a relatively constant percentage of diastolic flow within the range of heart rates observed In the patients with more severe mitral stenosis (mitral valve areas less than 1 0 cm) effective atrial contraction is noted to contribute a greater percentage to diastolic filling at the more rapid heart rate

The increased diastolic flow across the stenotic mitral valve as a result of active atrial transport is reflected as an incremental increase in stroke volume occurring during the subsequent ventricular contraction The study by Kendall and colleagues noted that the absolute and percentage contribution to stroke volume by a properly timed atrial contraction was essentially constant at heart rates of 80 to 120 per minute for patients with moderate mitral stenosis In two patients with more severe mitral stenosis active atrial transport contributed substantially more to stroke volume in both absolute and percentage terms as the heart rate increased to 150 beats per minute Consideration of the results of the present study in conjunction with those of Kendall and colleagues allows the complimentary hemodynamic relationship between increased mitral diastolic flow and the subsequent increase in stroke volume to be better appreciated

Duplicate cardiogreen dye indicator dilution cardiac outputs were compared in two patients with the cardiac outputs calculated from the simultaneously measured mitral valve gradient This procedure was carried out in order to justify the assumption that the stenotic mitral valve can be considered a fixed orifice obstruction In addition agreement between the measured cardiac output and the calculated cardiac output validated the technique of using changes in mitral valve gradient to predict changes in integrated cardiac output

The necessity of measuring the hemodynamic effects of acute interventions prior to the compensatory effects of homeostatic mechanisms is also emphasized by the measurement of simultaneous cardiac output in this study The acute loss of atrial transport activity during synchronous atrioventricular pacing (State 4) resulted in a decrease in both the calculated and observed cardiac output by approximately 18 per cent at both heart rates These results are at variance with results reported by Carleton and Graettinger

er[1] in which no demonstrable change in cardiac output was observed between atrial and synchronous atrioventricular pacing in patients with mitral stenosis It should be noted that our observations were made within 15 seconds of withdrawal of effective atrial systole prior to the time when compensatory effects of homeostatic mechanisms could intervene In the work by Carleton and Graettinger more than three minutes elaspsed from the onset of synchronous atrioventricular pacing until cardiac output measurements were made During this period there was sufficient opportunity for homeostatic mechanisms to obscure the contribution of atrial systole to integrated cardiac output in patients with mitral stenosis These observations therefore demonstrate the over all importance of the intact circulatory system as the primary determinant of cardiac output

The pathophysiological relationships which exist between heart rate, mean mitral valve gradient mitral diastolic flow integrated cardiac and left ventricular ejection time as documented in this study are illustrated in Fig 8 At both heart rates effective atrial transport augments the mean mitral valve gradient by approximately 40 per cent In order for cardiac output to be maintained at the faster heart rate the mean mitral valve gradient must be increased by 50 per cent from 11 to 16 mm Hg The mitral valve gradient is comprised of two components (1) the contribution of active atrial transport which increases from 4 to 6 mm Hg and (2) the contribution of passive atrial transport which increases from 7 to 9 8 mm Hg as the heart rate is increased Thus it can be appreciated that the contribution of active and passive atrial transport to the total mitral valve gradient increases in a pari passu fashion Likewise withdrawal of effective atrial transport decreases the diastolic flow per beat and the cardiac output by 20 per cent at both heart rates in patients with mitral stenosis There is an associated reduction in left ventricular ejection time of 11 per cent indicating a concomitant reduction in stroke volume In addition the presence of effective atrial systole in patients with mitral stenosis has been demonstrated to maintain cardiac output at lower levels of left atrial mean pressure than would be otherwise present in patients with mitral stenosis and atrial fibrillation under comparable conditions of mitral valve flow The beneficial effect of maintaining active atrial transport in patients with mitral stenosis has been demonstrated by this study

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His bundle electrocardiography in manifest and concealed right bundle branch extrasystoles

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Few authors have discussed the value of His bundle electrograms in the diagnosis of right bundle branch ectopic beats Only six possible examples of right bundle branch extrasystoles have appeared in isolated reports (Table I) This communication therefore is justified since it deals with the electrophysiological findings in patients with concealed and manifested impulses probably arising in the right bundle branch

Materials and methods

His bundle recordings were performed as previously described after explaining the procedure to and obtaining written consent from 28 symptomatic patients referred to the Cardiovascular Laboratory for electrophysiological studies The criteria of the New York Heart Association were used for diagnosis of complete and incomplete bundle branch block patterns in both conducted and ectopic beats All patients except the one with digitalis toxicity (Patient No 10 in Table II) were off medications for at least 48 hours before the procedure

During sinus rhythm A and H represented the onset of atrial and His bundle deflections in the His bundle electrographic (HBE) lead V was the beginning of ventricular depolarization in whichever lead (intracardiac or surface) it occurred first The A H and H V intervals were measured by the conventional method The normal ranges in our laboratory are 55 to 120 msec and 35 to 55 msec respectively In all patients except those shown in Figs 7 and 8 three surface leads were recorded simultaneously with the intracardiac leads The diagnosis of impulse formation in the right bundle branch was made according to the criteria of Puech and Grolleau[1] Rosenbaum and colleagues[6] and Massumi and associates[3] as will be discussed subsequently For the purpose of this presentation beats arising in the His bundle were considered supraventricular whereas those arising below the bifurcation were considered ventricular

After the diagnostic part of the procedure was terminated 13 patients received two intravenous (100 mg) boluses of lidocaine five minutes apart The total number of ectopic beats was determined (by recording at low paper speeds) at two five minute intervals The control preceded the first bolus of lidocaine The effects of this drug were assessed five minutes after the end of the second bolus

Results

Right bundle branch ectopic beats in patients without bundle branch block Ten patients with narrow QRS complexes had premature or escape beats with the following characteristics (1) QRS complexes of different contour from those of sinus beats not preceded by normal or abnormal P waves (2) incomplete left bundle block pattern

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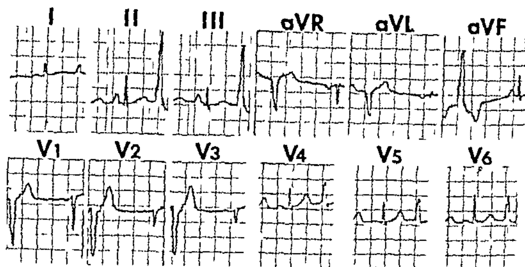


Fig 1 Right bundle branch extrasystoles in a patient without bundle branch block

Table I Possible examples of impulse formation in right bundle branch (from the literature, all values in msec)

Study	*Sinus QRS*	*Sinus H V*	*Ectopic QRS*	*Ectopic H V*	*Alternate site*
Puech (Ref 1 Fig 43)	CLBBB	Normal (not stated)	CLBBB	Slightly shorter than normal (not stated)	(a) Distal His bundle (b) Proximal LBB
Puech (Ref 1 Fig 44)	CLBBB	50	ILBBB	20 40	None
Zipes and Fisch (Ref 3 Fig 4)	IRBBB	30	ILBBB	20	None
Jacobson and Scheinman (Ref 2 Fig 2)	CLBBB	60	CLBBB	50	(a) Distal His bundle (b) Proximal LBB
Puech (Ref 1 Fig 66)	Normal	50	ILBBB	25	None
			CLBBB	10	None
Curtiss et al (Ref 4 Fig 4)	Normal	50	CLBBB	10	None
	CRBBB & LAH	65	CLBBB	20 40	None

CLBBB = complete left bundle branch block ILBBB = incomplete left bundle branch block CRBBB = complete" right bundle branch block IRBBB = incomplete right bundle branch block LBB = left bundle branch LAH = left anterior hemiblock

with QRS duration of less than 120 msec and (3) retrograde activation of the His bundle occurring close to, or less than 35 msec after the onset of ventricular depolarization in whichever lead it occurred first (Table II and Figs 1 and 2)

The morphology of these ectopic beats suggested a right bundle branch origin from which the impulse proceeded antegradely to the right ventricle and retrogradely to the His bundle finally reaching the left ventricle through the left bundle branch system [1] Although activation of right ventricle started before that of left ventricle the asynchrony was less than if the impulse had originated in the free right ventricular wall and had to traverse the septum in a right to left direction This explains why the QRS complexes showed an incomplete left bundle branch block pattern only 10 to 20 msec wider than those of sinus origin [11]

It should be stressed that the H V interval did not give a measure of linear retrograde conduction time from V to His bundle [6] Rather it reflected differences in arrival of excitation at the ordinary right ventricular muscle and at the His bundle In patients without conduction defects in *the right bundle branch* the position of the H deflection relative to the beginning of ventricular depolarization as well as the QRS morphology is influenced by the more proximal or distal location of the pacemaker within the right bundle branch (the lower the pacemaker the longer the duration of V H interval and QRS complex) *This statement however might not necessarily* apply in patients with conduction defects in the right bundle branch as will be discussed in the corresponding section

The ectopic beats in Figs 1 and 2 and Table I, were not His bundle impulses with left bundle branch block aberration since in this case the H V *interval would have been similar to* [ ] or slightl

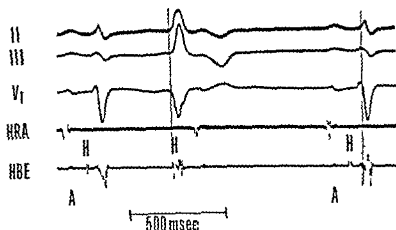


Fig 2 Right bundle branch extrasystoles in a patient without bundle branch block *HRA* = high right atrium *HBE* = His bundle electrographic lead *H* = retrograde His bundle deflection

Table II Clinical and electrocardiographic information in patients with right bundle branch ectopic beats who did not have bundle branch block (all values in msec)

							Ectopic right bundle branch beats			
			Sinus beats							
Case No	*Age*	*Clinical diagnosis*	*A H (55 120)*	*H V (35 55)*	*QRS duration*	*QRS axis*	*V H interval*	*QRS duration*	*QRS axis*	*Timing*
1	22	MVP†	65	45	75	+45	0	100	+80	Premature
2	5	SSS	95	45	95	+40	−5	105	+75	Premature
3	5	PCSD	115	40	90	+60	−10	110	+80	Premature escapes
4	28	MVP	95	45	80	+30	0	100	+80	Premature
5	34	MVP	100	50	95	+50	−20	115	+65	Premature
6	53	NHD	75	50	0	0	+5‡	80	+30	Premature
7	44	MVP	110	45	0	−[illegible]0	−10	110	0	Premature
8	49	NHD	90	45	90	+15	+10	80	+140	Premature
9	53	ASHD	105	50	95	−[illegible]0	−10	115	0	Escapes
10	54	Dig	115	35	80	−15	−15	115	+30	Paroxysmal tachycardia

Normal ranges in our laboratory
†Abbreviations MVP = mitral valve prolapse SSS = sick sinus syndrome PCSD = primary conducting system disease NHD = no heart disease ASHD = atherosclerotic heart disease Dig = digitalis toxicity
‡H preceded V by 5 and 10 msec respectively

longer than those of conducted sinus beats Moreover impulse formation in the peripheral Purkinje network of the right ventricle would be expected to show V H intervals of at least 35 msec (minimal duration of antegrade H V interval in our laboratory) assuming that both forward and retrograde right bundle branch conduction times had similar values Ectopic beats from other sites were not observed in these ten cases

Right bundle branch ectopic beats in patients with complete right bundle branch block Four patients had a right bundle branch block pattern (QRS duration greater than 120 msec) with a normal electrical axis (Table III and Fig 3) and normal H V intervals Three of the four patients had primary conducting system disease with prolonged A H intervals The premature beats showed an incomplete left bundle branch block morphology (QRS duration of less than 120 msec) with V H intervals ranging between 0 and 15 msec The site(s) or origin within the right bundle branch of the extrasystoles in these four cases will be discussed in the corresponding section Ectopic ventricular beats from other sites were not observed in these patients during the procedure

In nine additional patients with right bundle

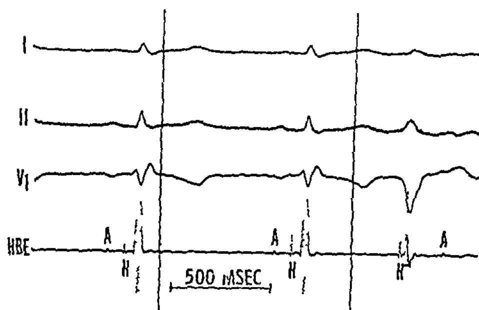


Fig 3 Right bundle branch extrasystoles in a patient with conduction delay or block in right bundle branch Intervals between two markers equal 1 000 msec

Table III Clinical and electrocardiographic information in patients with right bundle branch block and right bundle branch ectopic beats

Case	*Age*	*Clinical diagnosis*	*A H*	*H V*	*QRS duration*	*QRS axis*	*V H interval*	*QRS duration*	*QRS axis*	*Timing*
11	23	ASHD	90	40	120	+50°	0	115	+60°	Premature
12	63	PCSD	170	50	140	+30	−10	110	+60	Premature
13	57	PCSD	220	50	150	+10	−15	115	+30	Premature
14	61	PCSD	190	50	130	+60°	−15	115	0	Premature

ASHD = atherosclerotic heart disease PCSD = primary conducting system disease

branch block presumably due to primary conducting system disease the right bundle origin of the extra beats could not be conclusively proved Although the ectopic QRS morphology resembled that of sinus beats the H V intervals were only 10 to 20 msec shorter (Fig 4) Thus impulse formation could have occurred in the proximal right bundle branch (above the site of block) as well as in the distal His bundle or proximal left bundle branch [11] Ectopic (ventricular) beats from other sites were recorded (during the procedure) in six of these patients (Fig 5) Four of these patients received lidocaine (Table IV)

Right bundle branch ectopic beats in patients with complete left bundle branch block In four patients with complete left bundle branch block attributed to primary conducting system disease the ectopic beats showed in comparison with sinus beats similar QRS morphology and slightly shorter (10 to 20 msec) H V intervals Therefore, it could not be determined whether these beats arose in the proximal right bundle branch distal His bundle or proximal left bundle branch (above the site of block) [1]

However, ectopic beats presumably originating in the right bundle branch were seen in a 62 year old female with primary conducting system disease (Figs 6 to 8) The electrocardiogram depicted in Fig 6 shows (a) frequent premature beats *(top strip)* (b) episodes of Type II (Mobitz) A V block *(middle strip)*, and (c) premature beats with unexpected P R prolongation *(bottom strip)*

In Fig 7 the duration of the A H and H V intervals in conducted beats was 125 and 60 msec , respectively These values are slightly above the normal limits in our laboratory Whereas the surface lead had (as the middle strip of Fig 6) the classical features of Type II, Mobitz A V block (in that the non conducted third and fifth P waves were preceded by P R A H and H V interval of constant duration) the HBE lead revealed the presence of premature His bundle depolarizations (H) preceding each non con

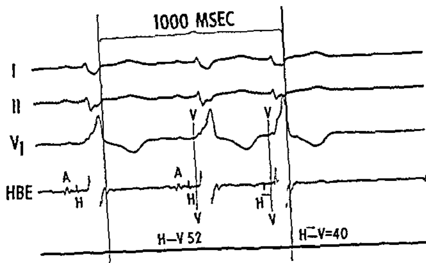


Fig 4 Patient with "complete" right bundle branch block and extrasystoles arising in either (a) distal His bundle (b) proximal left bundle branch, or (c) right bundle branch proximal to the affected area

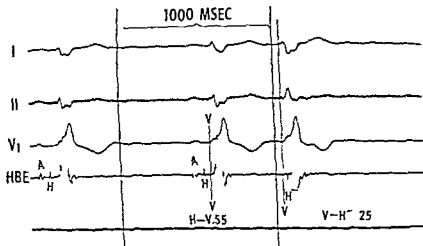


Fig 5 Same patient as in *Fig 4* Left anterior fascicular extrasystoles in a patient with "complete" right bundle branch block

ducted atrial electrogram Thus failure of the third P wave to reach the ventricles and of the fifth to activate the His bundle could have been due to the concealed refractoriness created by H at the distal His bundle (or right bundle branch) and the A V node respectively (pseudo A V block secondary to concealed His depolarizations)

Fig 8 depicts a sinus beat followed by an extrasystole The H V interval preceding the latter (30 msec) was shorter than that of the former (60 msec) This finding suggests that impulse formation occurred in the right bundle branch rather than in the His bundle or proximal left bundle or peripheral right ventricular muscle

Retrospectively the premature His bundle depolarizations and the pseudo A V block in Fig 7 could have resulted from impulse formation in the right bundle branch with conduction block towards the ventricles and propagation towards His bundle

Effects of Lidocaine This drug reduced the incidence of ectopic beats in two of the five patients with narrow QRS complexes while being ineffective in two other cases (Table IV) Its action could not be assessed in one patient

In contrast the number of ectopic beats was significantly reduced in all but one of the eight patients with "complete" right bundle branch block to whom lidocaine was given (Table IV)

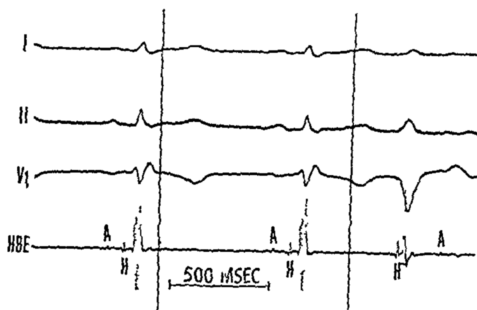


Fig 3 Right bundle branch extrasystoles in a patient with conduction delay or block in right bundle branch Intervals between two markers equal 1 000 msec

Table III Clinical and electrocardiographic information in patients with right bundle branch block and right bundle branch ectopic beats

Case	Age	Clinical diagnosis	A H	H V	QRS duration	QRS axis	V H interval	QRS duration	QRS axis	Timing
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12	63	PCSD	170	50	140	+30	−10	110	+60	Premature
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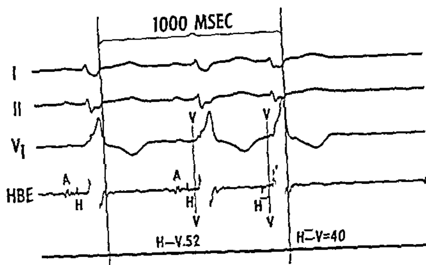


Fig 4 Patient with complete right bundle branch block and extrasystoles arising in either (a) distal His bundle (b) proximal left bundle branch or (c) right bundle branch proximal to the affected area

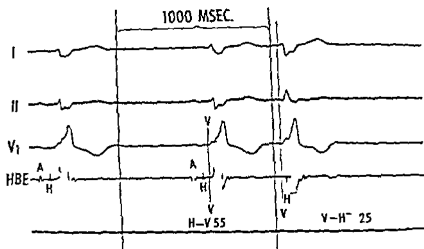


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Table IV Effects of lidocaine on right ventricular ectopic beats

Patient no	*Before*	*After*
Patients with narrow QRS complexes		
Case 6	6	6
Case 7	12	3
Case 8	4	6
Case 9	1	0
Case 10	33	0
Patients with complete right bundle branch block		
Case 11	6	1
Case 12	3	0
Case 13	0	2
Case 14	8	0
*Patients with *incomplete right bundle branch block*		
Case 15	14	7
Case 16	7	2
Case 17	23	0
Case 18	16	0

Includes ventricular beats which could have arisen in proximal right bundle branch distal His bundle or proximal left bundle branch plus all other ventricular beats

Discussion

Impulse formation within the right bundle branch in patients without bundle branch block The ectopic beats in Table I and Fig 1 fulfilled the electrocardiographic criteria of Rosenbaum and associates[1] for the diagnosis of right bundle branch extrasystoles It should be stressed that the exact origin could not be proven conclusively from the HBE lead but had to be inferred from the coexisting changes in the surface leads[1] Obviously His bundle pacing cannot be performed for validation of a deflection within an intermittent ectopic beat In these cases having recorded a right bundle electrogram following the missed (due to technical reasons) H deflection of a His bundle (A V junctional) beat with aberration was excluded because the right bundle deflection would have occurred at its normal interval when appearing in front of a QRS complex with an incomplete left bundle branch pattern and not at (or slightly after) the onset of ventricular depolarization

In our Cardiovascular Laboratory the polarity of the deflection has been of no help in determining whether the impulse traversed the corresponding structure in a forward or retrograde direction[5,8]

Impulse formation within the right bundle branch in patients with right bundle branch block Other factors in addition to the more proximal or distal (high or low) site of origin have to be considered when attempting to diagnose impulse formation within the right bundle branch in the presence of complete right bundle branch block For example, the location (high or low) of the conduction defect and nature of the latter (either conduction delay or block anterograde retrograde or both) can also influence both QRS duration and the interval between H and V[11] (Fig 9)

Thus the ectopic beat in Fig 3 could have arisen in the right bundle branch below the affected area But this would have required absent, or minimal retrograde conduction delay (Fig 9B) An alternative explanation is impulse formation within the affected (low or high) area in the right bundle branch with coexisting differential conduction delays[11] from site of origin to His bundle and ventricles respectively (Fig 9C and D)

Therefore in patients with conduction delay, or block, within the right bundle branch the position of H relative to V as well as QRS morphology is not only determined by the more distal or proximal location of the pacemaker but by the variations of the spread of activation into the His bundle and ventricles (Fig 9)[1] Similar doubts regarding the classification of A V rhythms into high, middle and low by the location of the P waves in relation to the ventricular complexes were expressed by Scherf and Shookhoff[13] in 1926

Ectopic impulse formation occurring proximally to an area of complete forward right bundle branch block can yield a QRS pattern similar to that of supraventricular beats but with H V intervals of slightly shorter duration than those of sinus beats[1] However more or less the same QRS morphology and H V interval are expected if impulse formation occurs in the low His bundle or in proximal left bundle branch[1] (Fig 5) Thus when complete (left or right) bundle branch block is present ectopic beats with QRS morphology of similar contour than that of sinus beats might reflect a supraventricular, A V junctional or His bundle (supraventricular) as well as a bundle branch-fascicular (ventricular) origin[1,11]

Moreover in beats arising below the affected area (within the right bundle branch) the duration of the QRS complexes and V H intervals will be prolonged if there is complete retrograde



Fig 6 Monitoring Lead II of a patient with complete left bundle branch block showing premature beats *(top)* pseudo Type II (Mobitz) A V block *(middle)* and abrupt unexpected P R prolongation *(bottom)* Conventional diagram was constructed according to the information supplied by the His bundle recordings (*see Fig 7 and 8)*

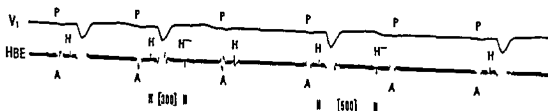


Fig 7 His bundle recording showing pseudo Type II (Mobitz) A V block due to concealed (in what regards surface leads) premature His bundle depolarizations which in turn would have resulted from impulse formation in the right bundle branch.

(bidirectional) block thereby resembling *true* right ventricular extrasystoles (those originating distal to the Purkinje myocardium junction)

Right bundle branch extrasystoles in patients with left bundle branch block Because in Fig 8 manifest right bundle extrasystoles were assumed to have been present it was inferred that in Figs 6 and 7 impulse formation occurred within the right bundle branch *and that* while conduction was blocked towards the ventricles *propagation* was possible toward the His bundle This pseudo A V block was attributed to the premature His bundle depolarizations *in turn* produced by impulses which after having originated in the right bundle branch were blocked towards the ventricles while being able to invade retrogradely the His bundle

This case is the fifth possible example of pseudo A V block produced by concealed extrasystoles arising below the bifurcation of the His bundle In three of these cases His bundle electrocardiography suggested a left bundle (or left fascicular) origin and in one case a right bundle origin

The slight difference in QRS morphology demonstrated by the early (manifest) extrasystoles (Figs 6 and 8) suggests that they reached the right ventricle before the relative refractory period of the latter had expired Alternatively the block in the left bundle branch might not have



Fig 8 Sinus beat (first QRS complex) followed by premature beat presumably arising in the right bundle branch

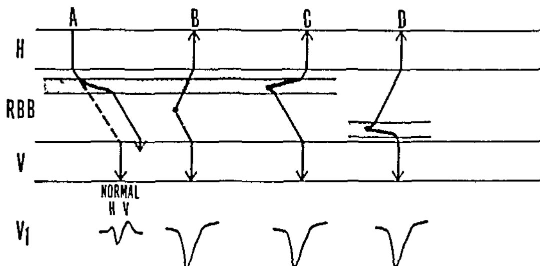


Fig 9 Diagrammatic representation of right bundle branch extrasystoles in the presence of significant conduction delay in the right bundle branch Vertical lines at H and V levels represent the onset of His bundle and ventricular depolarization respectively Oblique lines at the right bundle branch *(RBB)* level indicate conduction through the RBB *(solid line)* and left bundle branch *(broken line)* Shaded rectangles are the areas of conduction delay V is the QRS morphology

been complete during sinus rhythm with part of the ventricle still being activated via the left bundle branch Therefore if the premature impulse reached the ventricles exclusively through the right bundle branch the resulting QRS complexes would have had a slightly different contour from those of the sinus beats

Nevertheless we should stress that the exact nature of the deflection appearing in front of the premature QRS complexes could not be determined with absolute certainty Although most probably His bundle in origin (in which case the beat under consideration indeed arose in the right bundle branch) it could also have been a right bundle branch electrogram preceded by the 'missed (due to technical reasons) H potential of a His bundle ('A V junctional) extrasystole But in the latter case a double conduction delay has to be postulated, one above the right bundle branch deflection accounting for the prolonged H RB interval of 30 msec, and another below it, explaining the longer than normal RB V interval of (also) 30 msec

Effects of lidocaine Lidocaine appeared to have been more effective in patients with complete bundle branch block than in those with narrow QRS complexes This could simply reflect the fact that the number of patients in each subgroup was rather small However the possibility that the mechanism of right bundle ectopic beats in patients with right bundle branch block might not be the same as in those with an intact bundle branch (hence explaining the differential effects of lidocaine) is an intriguing possibility that awaits further study

Summary

His bundle electrocardiography was helpful in the diagnosis of impulse formation in the right bundle branch Ten patients with narrow QRS complexes had ectopic beats with an incomplete left bundle branch pattern and almost

simultaneous activation of His bundle and ventricles Both QRS morphology and H V intervals depended on the more proximal or distal location of the ectopic focus In four patients with complete right bundle branch block the morphology of ectopic ventricular complexes and H V intervals also depended on the presence or absence of retrograde block and differential degrees of forward and/or retrograde conduction delays Nine patients with complete right bundle branch block and four with complete left bundle branch block had premature beats which could have originated in the proximal right bundle branch proximal left bundle branch or distal His bundle In one patient with complete left bundle branch block concealed His bundle depolarizations (probably originating in an ectopic focus located in the right bundle branch) produced pseudo Type II (Mobitz) A V block Although lidocaine appeared to have been more effective in patients with bundle branch block than in those with narrow QRS complexes further studies are necessary to corroborate this impression

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The electrocardiographic response to maximal treadmill exercise of asymptomatic men with left bundle branch block

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Exercise electrocardiography has been demonstrated to be a valuable tool in the identification of men with a high risk for developing coronary atherosclerotic heart disease (CAD)[1-3] The identification of persons who have latent CAD is extremely important when dealing with flying personnel whose health is critical to public safety These fliers represent large financial investments because of their expensive training continuing education, and on the job experience[4] Therefore every effort should be made to retain aircrewmen who are not at high risk for sudden incapacitation

In a follow up study of asymptomatic USAF flying personnel with left and right bundle branch block prognosis was dependent on associated cardiovascular disease[5] Also cardiac catheterization studies of apparently healthy individuals with left bundle branch block (LBBB) have shown a low prevalence of angiographic CAD[6] Most clinical studies dealing with LBBB have given a rather bleak prognosis for individuals with this conduction abnormality mainly because the populations studied were symptomatic patients[8-10] In contrast asymptomatic men with LBBB without evidence of cardiovascular disease have not demonstrated an increased risk for sudden incapacitation Therefore aircrewmen with LBBB normal medical evaluations normal noninvasive studies and normal cardiac catheterizations have been maintained on flying status Their flying status has been contingent on successfully completing annual noninvasive reexaminations at the USAF School of Aerospace Medicine (USAFSAM)

Individuals with LBBB are a special group of patients with respect to electrocardiographic exercise testing ST segment and T wave changes present at rest have created uncertainty with respect to the interpretation of the repolarization response to exercise testing Some investigators have used LBBB as a criterion to completely exclude patients from exercise testing[11, 12] whereas others have stated it does not interfere with the interpretation of the test[13, 14] Those investigators who report that CAD can be diagnosed from exercise induced electrocardiographic changes in testing patients with LBBB have suggested that the degree of ST segment depression was markedly greater in those patients with significant CAD than in LBBB patients without CAD[15] The most recent study concluded that an additional −0 15 mv of ST segment depression should be used as the criterion for an abnormal response to

The research reported in this paper was conducted by personnel of the Clinical Sciences Division USAF School of Aerospace Medicine Brooks AFB Texas

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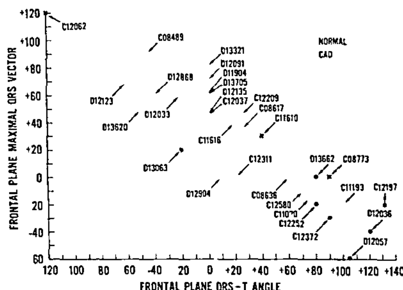


Fig 1 The frontal plane QRS-T angle and the mean frontal plane QRS axis as measured in the resting 1? lead electrocardiogram of the 31 men with LBBB

exercise testing in the presence of LBBB This additional amount of ST segment depression (greater than that present at rest) was considered to be very suggestive of CAD This study presents the experience at USAFSAM with maximal treadmill exercise testing (MTMT) of asymptomatic men with LBBB

Methods

This study deals with 31 asymptomatic aircrewmen with LBBB evaluated at USAFSAM The patients were all referred to USAFSAM for evaluation of LBBB which was found as a serial change on annual electrocardiograms Standard criteria were used for diagnosing LBBB All patients were asymptomatic and considered themselves to be in excellent health All 31 had cardiac catheterization performed as an elective procedure to rule out CAD as a possible etiology for the LBBB and enable them to continue on flying status

During the evaluation the following studies were performed in a standardized manner medical history physical examination chest roentgenogram blood chemistry profile resting electrocardiogram vectorcardiogram Holter monitoring maximal treadmill test and cardiac catheterization Maximal treadmill testing was performed using a constant speed of 3 3 miles per hour (90 meters per minute) and an increasing incline of 1 0 per cent each minute or 5 per cent each three minutes [13, 9] The monitoring Lead CC_5 consisted of anodized silver-silver chloride electrodes placed at the left and right anterior axillary line at the fifth intercostal space level Comparison studies have shown this bipolar lead to give ST segment amplitude and slope measurements comparable to Lead V_5 [2] Meticulous skin preparation kept impedance levels to 5 000 ohms or less as checked by an alternating current impedance meter The CC_5 lead data were recorded pre exercise with the subject supine and standing then continuously during and for eight minutes after exercise All electrocardiographic signals were recorded on electrocardiographic paper and stored on analog magnetic tape Indirect cuff blood pressure measurements were obtained throughout the procedure All patients were encouraged to perform a maximal effort and oxygen consumption measurements were made as previously described [3, 9]

Almost all the cardiac catheterizations were performed at USAFSAM However a few of the first procedures were performed at Wilford Hall USAF Medical Center Cardiac catheterization was performed via a right brachial arteriotomy Left ventricular end diastolic pressure was measured and then left ventricular angiography was accomplished in the right anterior oblique position Selective coronary angiography was per

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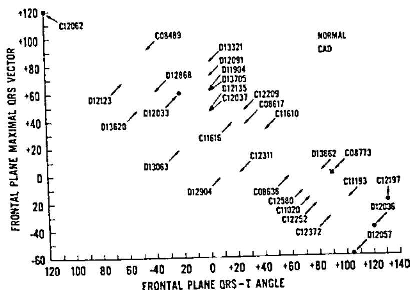


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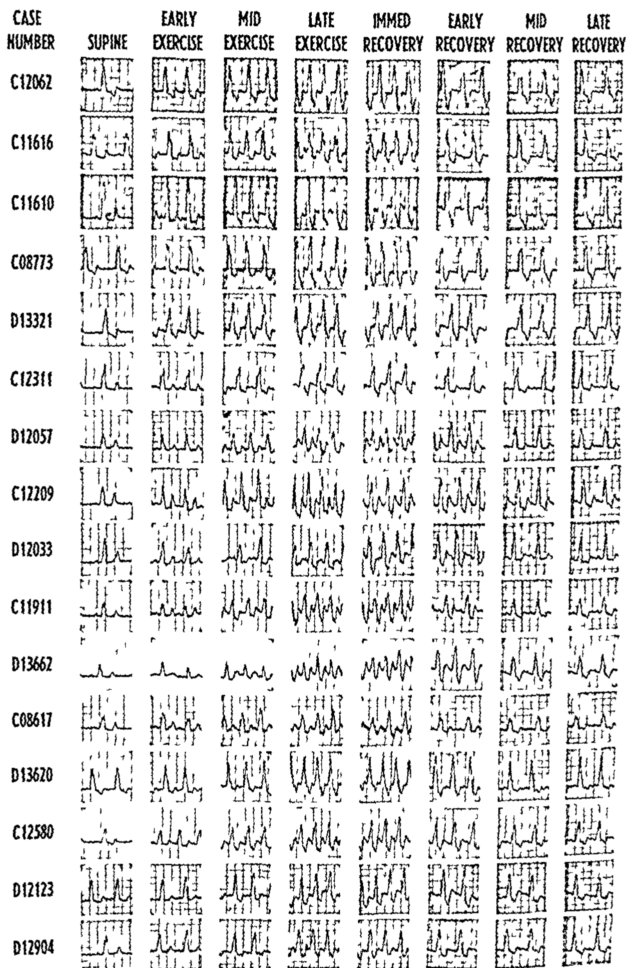


Fig 2 The actual electrocardiographic tracings of bipolar Lead CC before and in response to maximal treadmill exercise in the 31 asymptomatic men with LBBB

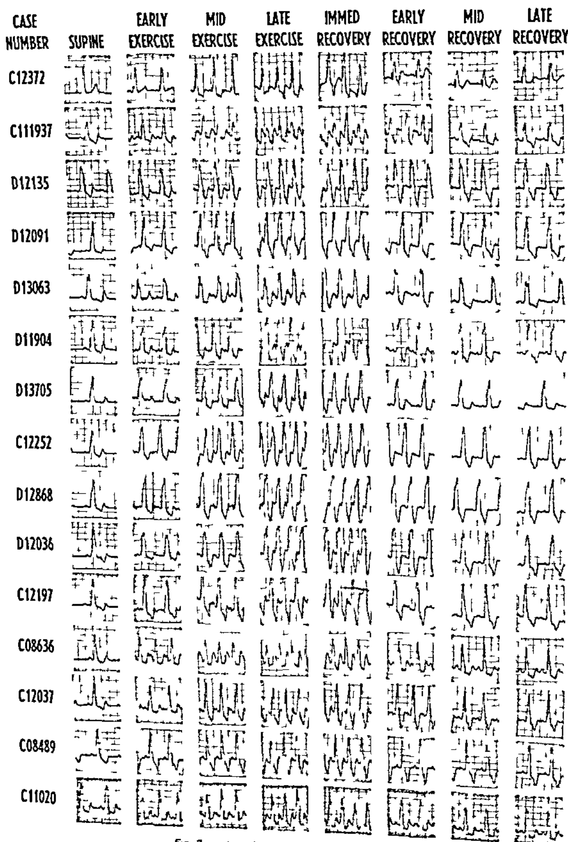


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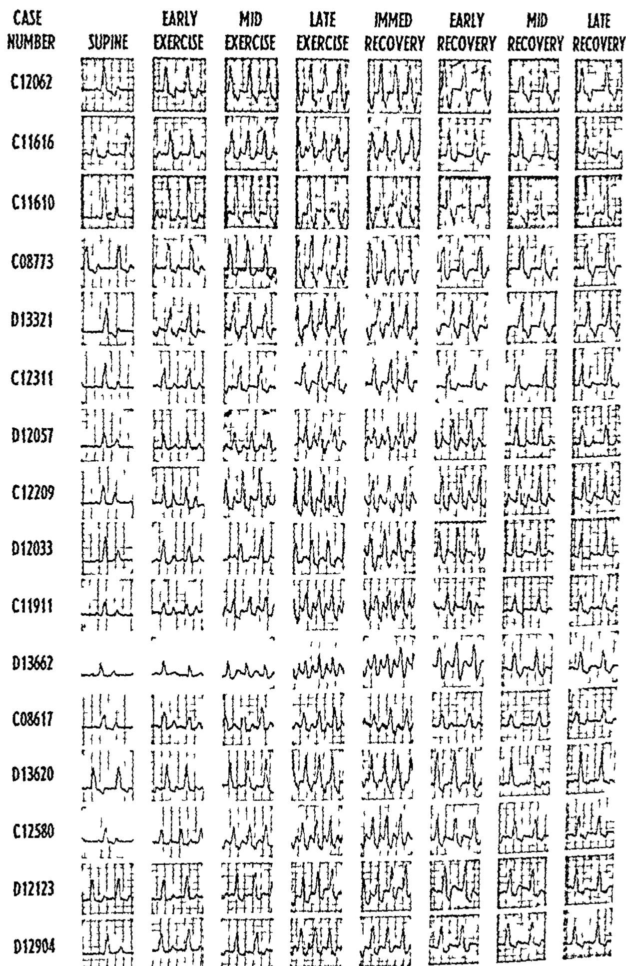


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Table II The means and standard deviations of the physiological parameters of the 31 asymptomatic LBBB subjects measured during their USAFSAM evaluation

	Age (yrs)	*Height (inches)*	*Weight (pounds)*	*Cholesterol (mg %)*	*Triglycerides (mg %)*	*Resting BP* (mm. Hg)*	*VO (c c/Kg min)*	*Max HR (beats/min.)*	*Max Systolic BP (mm Hg)*	*Double product†*
CAD	44	70	165	[illegible]	119	131 (11) / 84 (10)	[illegible]	186	195	36.1
(N = 5)	(5)	(2)	([illegible])	(20)	([illegible])		([illegible])	(9)	(26)	(4.1)
Normal	41	70	175	216	120	129 (1[illegible]) / 81 (9)	38	190	195	35.0
(N = 26)	(6)	(2)	([illegible])	([illegible])	(40)		(5)	(11)	(26)	(5.3)

Abbreviations M x = maximal BP = blood pressure HR = heart rat
†Doubl product = Max SBP × Max HR/10³

Table III The means and standard deviations of additional ST segment depression from the supine pre-exercise measurements in the LBBB subjects induced by maximal treadmill exercise (millivolts in Lead CC_5)

	Exercise			*Recovery*			
	Early	*Mid*	*Late*	*Immediate*	*2 Min*	*5 Min*	*8 Min*
CAD	–0.14	–0.27	–0.48	–0.50	–0.38	–0.16	–0.12
(N = 5)	(0.0[illegible])	(0.05)	(0.06)	(0.07)	(0.13)	(0.07)	(0.05)
Normal	–0.09	–0.24	–0.42	–0.48	–0.33	–0.12	–0.09
(N = 26)	(0.08)	(0.11)	(0.21)	(0.23)	(0.20)	(0.0[illegible])	(0.0[illegible])

graphic CAD and the remaining 25 were normal None of the 31 subjects had overt evidence of cardiac dysfunction though some had a mild elevation of their left ventricular end diastolic pressure and/or an abnormality of their left ventriculogram However these findings were not of such a nature to be diagnostic of a cardiomyopathy

The physiological parameters obtained during the USAFSAM evaluation of the 31 men are presented in Table II Using Student s unpaired t tests no significant differences were found between the five men with significant angiographic CAD and the 26 men work with normal studies The maximal oxygen consumptions and double products of the two groups were well within the range found in previous studies of our healthy aircrew population[3, 23]

Fig 1 illustrates the frontal plane QRS-T angle and the mean frontal plane QRS axis of the men from the study The QRS-T angle was determined as negative or positive by clockwise reference to the QRS vector This figure is included since it has been suggested that left axis deviation and a wide QRS-T angle make LBBB more likely secondary to CAD In this study left axis deviation and/or a wide QRS–T angle were found even in those felt to have benign LBBB

Fig 2 shows the actual recorded electrocardiograms of bipolar Lead CC_5 at rest and in response to maximal treadmill exercise The first five men at the top of the figure are those with significant angiographic CAD Table III lists the means and standard deviations of the additional ST segment depression during and after maximal treadmill exercise from the pre exercise CC_5 measurements (in millivolts) Using Student s unpaired t tests no significant differences were found between the two groups of men in regard to their ST segment response to treadmill exercise

Fig 3 shows the means and ranges of the actual amount of ST segment depression in the two groups for each time period A similar pattern of the time occurrence and amount of ST segment depression was found for both groups This figure shows clearly that a considerable amount of ST segment depression occurs in most subjects with LBBB in response to maximal treadmill exercise irrespective of whether or not they have CAD The mean amount of maximal absolute ST segment depression was about –0.5 mv for both groups and the individual with normal coronary

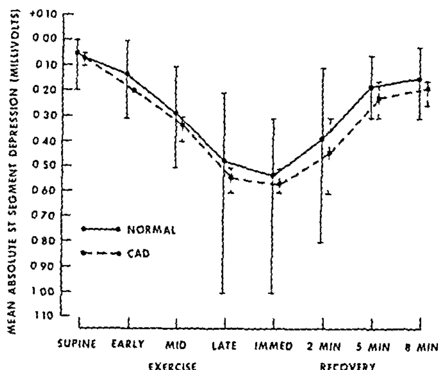


Fig 3 The means and ranges of the actual amount of ST segment depression for each time period in the two groups of LBBB subjects

Table I The five asymptomatic men with LBBB who were found to have significant angiographic coronary artery disease with a listing of the coronary arteries involved

Case number	*Number of coronary arteries and particular arteries involved with 50% or greater lesions*
C 12062	2 vessel disease (left circumflex and right coronary arteries)
C 11616	3 vessel disease (left main and right coronary arteries)
C 11610	1 vessel disease (left circumflex coronary artery and multiple less than 50% lesions in the right coronary artery)
C 08773	2 vessel disease (left main and left circumflex coronary arteries)
C 13321	3 vessel disease (left circumflex left anterior descending and right coronary arteries)

formed using the Sones technique [1] Multiple injections of both right and left coronary arteries were done in multiple views and recorded on 35 mm cinefilm Nitroglycerin was given before coronary injections and no coronary spasm was encountered Significant angiographic CAD was defined as the presence of an atherosclerotic lesion compromising 50 per cent or more of the luminal diameter in any major branch of the three main coronary artery systems

The original electrocardiographic treadmill exercise tracings were available on most patients However, in several instances the treadmill tracings were obtained from the magnetic tape recordings The ECG tracings were reviewed independently by three investigators (J E W A J S, and V F F) The amount of ST segment depression was obtained from visually averaging the amount of depression over a 10 to 20 second segment of the patient s tracing at the following time intervals supine in the pretest period at early exercise (usually two minutes into the exercise test) at midexercise (one half of the maximum total treadmill time), in late exercise (usually the final minute of exercise), in the immediate recovery and at two five and eight minutes of recovery

Most of the patients have undergone multiple annual medical evaluations at USAFSAM since the initial discovery of LBBB and have remained unchanged with respect to their electrocardiographic findings and other noninvasive studies

Results

The 31 asymptomatic men were divided according to their coronary angiographic findings Five asymptomatic men listed in Table I and identified by their USAFSAM case number were found to have significant angiographic CAD that could possibly be the etiology of their LBBB One of the men was found to have minimal angio

LBBB Our sample size was not large enough to state categorically that there can be no difference in the ST segment response of CAD patients with LBBB and those without CAD However it was of interest to compare the two groups of subjects No statistically significant differences were found between the two groups and therefore treadmill testing could not be used to distinguish those with CAD It is our conclusion that apparently healthy asymptomatic men with acquired LBBB can have considerable ST segment depression in response to maximal treadmill testing and that their ST segment response cannot be used to make diagnostic decisions about them These ST segment changes in CC_5 are in contrast to our findings in right bundle branch block patients [12]

Summary

This study presents the results of maximal treadmill testing and coronary angiography in 31 asymptomatic USAF aircrewmen with acquired left bundle branch block There were two sub groups 26 men with normal coronary angiography and five men with significant angiographic coronary angiography and five men with significant angiographic coronary artery disease The mean amount of maximal ST segment depression induced by treadmill exercise was −0 5 mv for both groups and the range in the normal sub group was −0 3 to −1 0 mv No significant differences were found between the groups We concluded that apparently healthy asymptomatic men with acquired left bundle branch block can have considerable ST segment depression in response to maximal treadmill testing and that their ST segment response cannot be used to make diagnostic decisions about them

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Discussion

Previous studies have suggested that asymptomatic men with LBBB are not in danger of sudden incapacitation as long as they do not have any manifestations of cardiovascular disease[5] Therefore, asymptomatic USAF aircrewmen with LBBB and normal cardiovascular evaluations, including coronary angiography, have been maintained on flying status Annual noninvasive evaluations at the USAFSAM Consultation Service have been required for them to remain on flying status Their cardiovascular evaluations have included maximal treadmill testing LBBB subjects have had a functional capacity, maximal heart rate and blood pressure response to maximal treadmill exercise comparable to our findings in normal aircrewmen[3, 4] However the LBBB subjects have routinely had considerable ST segment depression in response to maximal treadmill testing

The main purpose of this report is to present the USAFSAM experience with the ST segment response to maximal treadmill testing of asymptomatic apparently healthy aircrewmen with LBBB This is especially pertinent since a recent report of 10 patients with LBBB stated that 0 15 mv or greater ST segment depression in response to treadmill exercise was abnormal[4] The investigators also concluded that the treadmill response of their patients agreed with their coronary angiographic findings Our report deals with 31 asymptomatic apparently healthy mean with acquired idiopathic LBBB all of whom had coronary angiography and thorough cardiovascular evaluations Five of them had significant angiographic CAD that possibly could explain their LBBB, though they were asymptomatic

No statistically significant differences were found between the men with and those without angiographic CAD in regard to their electrocardiographic findings at rest or in response to maximal treadmill exercise The failure to find a difference could be due to the small number of men with CAD and to the fact that their disease was functionally mild since they were asymptomatic However the important finding was that apparently well, asymptomatic men with LBBB can have considerable ST segment depression in response to maximal treadmill exercise The range of maximal ST segment depression in the 26 men without significant CAD was from −0 3 to −1 0 millivolts Since their physical examinations were entirely normal and their functional capacity and their heart rate and blood pressure response to maximal treadmill exercise were normal, the diagnosis of cardiomyopathy could not be made in any of these men In view of these findings, it is our contention that the ST segment response to maximal treadmill exercise cannot be used to make diagnostic decisions about men with LBBB

The pathogenesis of LBBB in our subjects remains unknown Studies have reported LBBB to occur in patients with CAD and hypertension although other etiologies such as focal fibrosis aortic valvular disease cardiomyopathy, sarcoidosis and various infectious processes have also been reported[24-28] There is a case report of a 40 year old man with Lenegre s disease who developed LBBB which progressed to complete heart block[29] LBBB in our subjects could not be related to any episodes with symptoms suggestive of CAD or myocarditis Thorough hemodynamic studies and left ventriculograms in men with LBBB have suggested some subtle abnormalities of myocardial function These findings could be due to delayed conduction secondary to LBBB rather than to subclinical heart muscle disease[25, 30] Our subjects had normal functional capacity and a normal heart rate and blood pressure response to maximal treadmill exercise which is evidence in favor of the integrity of their cardiovascular system

All the reported subjects had at least one normal electrocardiogram in their medical records before the onset of their conduction abnormality For this reason and because of the increasing prevalence of LBBB with increasing age it is unlikely that LBBB is often of congenital origin Approximately 20 per cent of our patients had intermittent LBBB at some time during their evaluations Intermittency has not been helpful in identifying those with or without CAD

This study has demonstrated that there can be a marked amount of ST segment depression in response to maximal treadmill testing in addition to that present during the pre exercise period in apparently healthy asymptomatic men with

LBBB Our sample size was not large enough to state categorically that there can be no difference in the ST segment response of CAD patients with LBBB and those without CAD However it was of interest to compare the two groups of subjects No statistically significant differences were found between the two groups and therefore treadmill testing could not be used to distinguish those with CAD It is our conclusion that apparently healthy asymptomatic men with acquired LBBB can have considerable ST segment depression in response to maximal treadmill testing and that their ST segment response cannot be used to make diagnostic decisions about them These ST segment changes in CC_5 are in contrast to our findings in right bundle branch block patients[3]

Summary

This study presents the results of maximal treadmill testing and coronary angiography in 31 asymptomatic USAF aircrewmen with acquired left bundle branch block There were two sub groups 26 men with normal coronary angiography and five men with significant angiographic coronary angiography and five men with significant angiographic coronary artery disease The mean amount of maximal ST segment depression induced by treadmill exercise was −0 5 mv for both groups and the range in the normal sub group was −0 3 to −1 0 mv No significant differences were found between the groups We concluded that apparently healthy asymptomatic men with acquired left bundle branch block can have considerable ST segment depression in response to maximal treadmill testing and that their ST segment response cannot be used to make diagnostic decisions about them

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Experimental and laboratory reports

A clinicopathologic study of prosthetic valve endocarditis in 22 patients Morphologic basis for diagnosis and therapy

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Endocarditis is a complication of valve replacement with prosthetic devices Prosthetic valve endocarditis is often lethal and early detection is crucial for successful therapy Recent clinical studies have reported successful treatment with antibiotics alone but stress the need for surgical intervention in refractory infection or with the onset of congestive heart failure or major embolic events

In this study we reviewed the clinical presentation and autopsy findings in 22 patients with prosthetic valve endocarditis studied at The Johns Hopkins Hospital over the past 17 years Our findings suggest that replacement of an infected prosthetic valve combined with antibiotic therapy should provide effective treatment for this otherwise frequently fatal complication of prosthetic valve surgery

Materials and methods

Twenty two autopsied patients from The Johns Hopkins Hospital who had prosthetic valve endocarditis following valve replacements were studied The clinical and autopsy records and the histological slides from autopsy and surgical pathology examinations were reviewed in each case Twenty one hearts were available for gross examination eight of them were studied following coronary arteriography and fixation in distention The conduction system was studied by serial histological sections in five patients

Results

Clinical data (Table I)

General The 22 patients ranged in age from 11 to 65 years (average 49 years) and nine were women Fourteen patients (64 per cent) had rheumatic heart disease four (18 per cent) calcific aortic stenosis two (9 per cent) bacterial endocarditis and one (4 per cent) valve disease of undetermined nature The aortic valve was replaced in 14 patients five (36 per cent) for regurgitation seven (50 per cent) for stenosis and two (14 per cent) for both The mitral valve was replaced in seven patients four (57 per cent) for stenosis and three (43 per cent) for stenosis and regurgitation One patient had severe aortic stenosis with mitral regurgitation and stenosis and required double valve replacement The following prostheses were used in the aortic position seven (50 per cent) Starr Edwards cage ball valves three (17 per cent) Bjork Shiley tilting disc valves two (14 per cent) Teflon cusp Bahnson valves one (7 per cent) homograft and one (7 per cent) Gott valve in the mitral position five (17 per cent) Starr Edwards cage ball valves one (14 per cent) Kay Shiley disc valve one Gott valve and one homograft In the pulmonic position one homograft was inserted All patients were placed on warfarin postoperatively Patient postoperative survival ranged from 20 days to four years with ten (45 per cent) living less than two months postoperatively and 12 (55 per cent) greater than two months In seven of the nine early deaths fever and symptoms were apparent from the initial postoperative days

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Fig 1 Aortic valve prosthetic endocarditis viewed from the left ventricle *Left* The inflammatory reaction has led to periprosthetic defects (probes) *Right* Dehiscence of most of the prosthetic suture line produced severe aortic regurgitation MV = anterior mitral valve leaflet IVS = interventricular septum

led to their endocarditis two patients had a second cardiac operation and one patient had had mediastinitis one a pneumonia the four others infections of the gum appendix urinary tract and skin re pectively

Pathological data

Source The offending organism was identified in 20 of the 22 cases Staphylococci were predominant accounting for seven (32 per cent) of the infections (four *Staphylococcus aureus* and three *Staphylococcus albus)* Gram negative organisms including Klebsiella Alkaligenes and Pseudomonas were responsible for four cases Diphtheroides for four and Streptococcus viridans for two Three patients had fungal infections including Aspergillus in two and Candida in one In two patients the organisms were not cultured during life but organisms were identified by bacterial stains of the infected material at autopsy In one patient the organism was a gram positive coccus in the other a gram negative rod A gross and histologic picture consistent with healed endocarditis without active infection was found at autopsy in four patients who had positive cultures for *Alkaligenes faecalis Staphylococcus albus Staphylococcus aureu* and *Streptococcus viridans* respectively and subsequent surgical and/or antibiotic therapy

Heart The hearts (Figs 1 to 8) ranged in weight from 330 Gm to 980 Gm 21 (95 per cent) were hypertrophied and 16 (73 per cent) had dilated left ventricles Fourteen of the hearts had a fibrous pericarditis consistent with the previous operation and two had a purulent pericarditis Prosthetic dysfunction was found in 17 patients (77 per cent) Valvular incompetence was the most common finding at the aortic site (Fig 1) present in nine of the 14 patients and was due to cusp destruction in three cases perivalvular leak in three poppet entrapment by thrombus in two and perforation of a ring abscess into right ventricle in one (Fig 2) Aortic annulus infection was identified in eight cases (57 per cent) and frank ring abscesses in three of them In two other patients ring infection had been present but in one a combination of antibiotic and surgical therapy and in another antibiotic therapy alone successfully treated the infection so that only chronic inflammatory reaction without organisms was seen at autopsy in each In five of the patients with annulus infection aortic regurgitation was present Aortic stenosis secondary to exuberant vegetations was present in one Valvular incompetence developed in the pulmonic homograft valve due to extensive cusp destruction

The most common form of prosthetic dysfunction in the mitral position was stenosis (Fig 6) which occurred in five of the six patients and resulted from extensive infected thrombus deposition (Fig 7) In the sixth patient mitral prosthetic incompetence developed on a homograft valve due to frank cusp destruction (Fig 8) Infection in the mitral annulus was present in three patients

Table I Prosthetic endocarditis Data in 22 patients

	Aortic valves	Mitral valve	Total
No of patients	15	7	22
Age range (avg) yrs	11 63 (48)	46 65 (52)	11 65 (49)
Sex M F	11 4	2 5	13 9
Postoperative period range (avg) months	1-48 (10)	1 20 (9)	1 48 (10)
No < 2 mos po	4 (27%)	1 (14%)	5 (23%)
No > 2 mos po	11 (73%)	6 (86%)	17 (77%)
Congestive heart failure	9 (60%)	4 (57%)	13 (59%)
Conduction block (po)	5 (33%)	0	5 (23%)
block due to endocarditis	3 (20%)	0	3 (14%)
Peripheral emboli at autopsy	13	7	20 (91%)
Prosthetic dysfunction	11 (73%)	6 (86%)	17 (77%)
Incompetence	10 (67%)	1 (14%)	11
Stenosis	1 (7%)	5 (71%)	6
Ring abscess	8 (53%)	3 (43%)	11 (50%)
Organism			
Gram positive†	9	4	13 (59%)
Gram negative	4	2	6 (27%)
Fungus	2	1	3 (14%)
Causes of death			
Congestive heart failure	7 (47%)	3 (43%)	10 (45%)
Emboli	2	3	5 (23%)
Ruptured aortotomy	2	0	2 (9%)
Sepsis	2	0	2 (9%)
Other	2	1	3 (14%)

Includes 1 pulmonary valve replacement
†Includes 4 Diphtheroids
po = postoperative

Clinical manifestations of endocarditis The initial clinical presentation in all patients was fever Positive blood cultures were obtained in 18 (82 per cent) of the 22 patients and in 14 (64 per cent) an organism was cultured from the blood during the initial hospital days In four patients (18 per cent) mediastinitis was associated with the endocarditis Three patients (14 per cent) presented with the stigmata of endocarditis such as a new murmur petechiae, Roth spots or splinter hemorrhages three with a major embolic event three with congestive heart failure and nine with only fever

Congestive heart failure developed in 13 patients (59 per cent) In five of these patients a new murmur suggested prosthetic dysfunction as the cause of the failure and was confirmed by cardiac catheterization in two patients Significant valve dysfunction was found at autopsy in all 11 patients who developed congestive heart failure In five patients (23 per cent) all with an aortic prosthesis, a conduction disturbance developed complete heart block in one, left bundle branch block in two and first degree block in two Although a presenting feature of only three patients a symptoms complex including fever chills, anemia a new murmur petechiae and hematuria eventually developed in 16 (73 per cent) patients, and a clinically identifiable embolic event was noted in eight (36 per cent) The diagnosis of endocarditis was made at some point in the hospitalization in 73 per cent of patients

Therapy Fifteen patients (68 per cent) received antibiotic therapy alone In six patients (27 per cent) reoperation was undertaken as well Four of these patients were in severe congestive heart failure and one was experiencing major embolic events These five patients all died within the first week following reoperation One patient underwent reoperation for refractory infection and lived for 12 months

Source of infection

Preoperative In two patients the source of infection related to the preoperative endocarditis for which the valve replacement was performed In one of these patients a postoperative mediastinitis developed and the organism cultured from the mediastinum was the same as that infecting both the natural and prosthetic valves

Operative In seven patients (32 per cent) the endocarditis originated within the perioperative period In two implanted material cultured at the time of operation grew out the offending organism The first of these patients developed mediastinitis and evidence of endocarditis within two weeks of operation The second did not develop symptoms of endocarditis until seven months later Three other patients developed mediastinitis postoperatively but whether the wound infections were causes or manifestations of endocarditis could not be determined The remaining two patients had persistent postoperative fever leukocytosis and positive blood cultures with no apparent source for their infection

Late postoperative Thirteen patients were discharged apparently well and subsequently developed endocarditis from approximately one month to two years postoperatively (average nine months) Although a specific source of the infecting organisms was not identified eight patients had postoperative complications which may have



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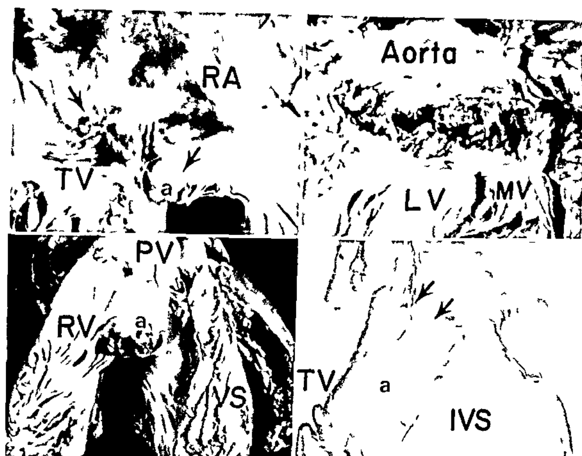


Fig 2 Aortic valve prosthetic ring abscess Severe infection surrounding aortic prosthesis producing a mycotic sinus of Valsalva aneurysm which perforated into the right ventricle *(RV)* through the crista supraventricularis *Upper left* Periprosthetic abscess (*a*) eroding into the right ventricle *(RV)* at the lower arrow and into the right atrium *(RA)* at the upper arrow *Upper right* Aortic valve ring abscess with prosthesis removed *Lower left* Perforation of abscess *(a)* through crista supraventricularis into the right ventricle outflow tract *Lower right* Histologic section through abscess *(a)* which has perforated between the arrows and under the tricuspid valve *(TV)* *into the right ventricle (Elastic stain original magnification ×5) IVS = interventricular septum PV* = pulmonary valve *MV* = mitral valve

(43 per cent) but no mitral perivalvular leaks were present In none of the 22 patients had the endocarditis spread to involve the other valves whether natural or prosthetic

Embolic myocarditis, abscesses and focal necrosis was seen in four hearts In two infection extended from the valve into the sinus of Valsalva and caused a mycotic aneurysm and in one of these the sinus of Valsalva aneurysms perforated into the right ventricle The aortotomy site was infected in two patients and in each of them led to fatal aortic wall rupture (Fig 3)

Conduction systems In the five patients in whom conduction disturbances developed in relation to endocarditis, or at some time during the postoperative period the conduction systems were examined In the patient with complete heart block the AV node and His bundle were obliterated by abscess (Fig 4) In two patients with first degree heart block the atrioventricular node was *extensively involved by the inflammatory* process extending from an aortic ring abscess but in both the bundle of His and both bundle branches were intact (Fig 5) The two patients with left bundle branch block showed no involvement of the conduction system by infection In both there was idiopathic atrophy and fibrosis of the proximal portion of the left bundle

Extracardiac Peripheral embolic events occurred in 19 patients (85 per cent) The spleen was affected in 13 patients (59 per cent) the kidneys in 11 (50 per cent) and the brain in 10 (45 per cent) In eight septic embolization was evident In five patients brain hemorrhages either subarachnoid or intracerebral were found

Causes of death Congestive heart failure was the leading cause of death in these patients accounting for 10 deaths (45 per cent) Systemic embolic events caused death in five patients (23 per cent) four due to cerebrovascular accidents and one due to multiple emboli to other organs

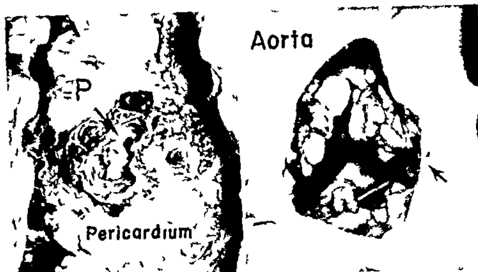


Fig 3 Aortic prosthetic endocarditis with ruptured aortotomy site *Left* The heart in situ at autopsy with a shaggy fibrinous pericarditis and an aortic perforation *(P)* surrounded by blood clot *Right* Exuberant vegetations seen from the aortic side of the prosthesis The perforation is at the end of the aortotomy site *(arrow)*

Pulmonary emboli caused death in one patient Other causes of death included ruptured aortotomy sites in two patients and persistent sepsis in two Death was sudden and unexplained in two patients in one prosthetic aortic stenosis had been caused by extensive vegetations and in the other sudden chest pain was followed by an idioventricular rhythm but no evidence of coronary emboli or infarction was evident at autopsy In the four patients in which active infection was not present at autopsy death was due to either intractable heart failure or embolic events from secondary prosthetic valve damage

Discussion

Endocarditis occurs on approximately 4 per cent of prosthetic valves and is usually fatal[5] In this study endocarditis in the immediate postoperative period had as its most common manifestation prolonged postoperative fever mediastinitis and positive blood cultures but recognition of endocarditis in the early postoperative period was frequently delayed in part due to fungal infection confusion with benign postoperative fever and diversion by infection in other areas (e g mediastinum) Gram negative bacteria and fungi were more common in the group of patients with early postoperative infection (57 per cent) than in the group of patients acquiring late infection (20 per cent) after discharge from hospital In general immediate postoperative endocarditis was a fulminant and rapidly progressive disease

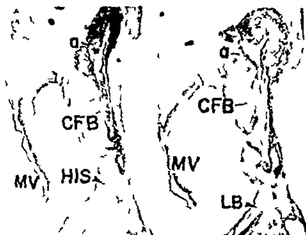


Fig 4 Complete heart block caused by valve ring abscess *Left* Histologic section showing the posterior extension of the aortic valve ring abscess *(a)* into the interatrial septum and along the central fibrous body *(CFB)* The His bundle has a marked loss of conducting fibers *Right* A more anterior section shows the abscess communicating with the left ventricular cavity through the central fibrous body The left bundle branches *(LB)* are intact *MV* = mitral valve (Both Hematoxylin and eosin original magnification ×5)

The patients with late postoperative endocarditis tended to have a more indolent slowly progressive disease All presented with fever and in most (82 per cent) positive blood cultures were obtained Although new murmurs and classic stigmata of endocarditis were not common at presentation an early diagnosis was usually made because of the high index of suspicion in patients with bacteremia and a prosthetic valve and an

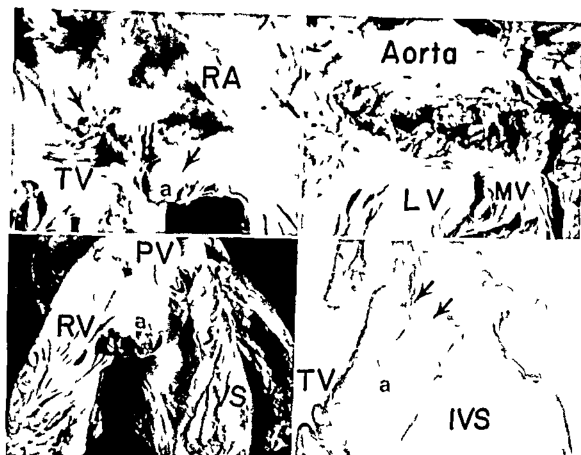


Fig 2 Aortic valve prosthetic ring abscess Severe infection surrounding aortic prosthesis producing a mycotic sinus of Valsalva aneurysm which perforated into the right ventricle *(RV)* through the crista supraventricularis *Upper left* Periprosthetic abscess *(a)* eroding into the right ventricle *(RV)* at the lower arrow and into the right atrium *(RA)* at the upper arrow *Upper right* Aortic valve ring abscess with prosthesis removed *Lower left* Perforation of abscess *(a)* through crista supraventricularis into the right ventricle outflow tract *Lower right* Histologic section through abscess *(a)* which has perforated between the arrows and under the tricuspid valve *(TV)* into the right ventricle (Elastic stain original magnification ×5) *IVS = interventricular septum* *PV* = pulmonary valve *MV* = mitral valve

(43 per cent) but no mitral perivalvular leaks were present In none of the 22 patients had the endocarditis spread to involve the other valves whether natural or prosthetic

Embolic myocarditis abscesses and focal necrosis was seen in four hearts In two infection extended from the valve into the sinus of Valsalva and caused a mycotic aneurysm and in one of these the sinus of Valsalva aneurysms perforated into the right ventricle The aortotomy site was infected in two patients and in each of them led to fatal aortic wall rupture (Fig 3)

Conduction systems In the five patients in whom conduction disturbances developed in relation to endocarditis or at some time during the postoperative period, the conduction systems were examined In the patient with complete heart block the AV node and His bundle were obliterated by abscess (Fig 4) In two patients with first degree heart block the atrioventricular node was extensively involved by the inflammatory process extending from an aortic ring abscess but in both the bundle of His and both bundle branches were intact (Fig 5) The two patients with left bundle branch block showed no involvement of the conduction system by infection In both there was idiopathic atrophy and fibrosis of the proximal portion of the left bundle

Extracardiac Peripheral embolic events occurred in 19 patients (85 per cent) The spleen was affected in 13 patients (59 per cent) the kidneys in 11 (50 per cent) and the brain in 10 (45 per cent) In eight septic embolization was evident In five patients brain hemorrhages either subarachnoid or intracerebral were found

Causes of death Congestive heart failure was the leading cause of death in these patients accounting for 10 deaths (45 per cent) Systemic embolic events caused death in five patients (23 per cent) four due to cerebrovascular accidents and one due to multiple emboli to other organs

Fig 7 Mitral stenosis caused by prosthetic valve fungal endocarditis. The mitral prosthesis was partly obstructed on the left atrial side by a mat of thrombus and fungus *(above)*. The infecting organism shown *below* was Aspergillus niger (Methenamine silver, original magnification ×250).

atrophy and fibrosis of the proximal left bundle and not to the aortic prosthetic endocarditis. Thus although conduction block may be a manifestation of prosthetic endocarditis it most often does not develop and when present may *not* necessarily be related to the infection.

Although Bahnson and colleagues showed the necessity of surgical intervention in cases of infected foreign material, the decision to reoperate on patients with prosthetic valve endocarditis is usually made with reluctance because it is felt that annulus infection is always present.[6] Poor suture retention by necrotic infected annulus and reinfection of the new valve are believed to be almost inevitable in surgical treatment of long-standing endocarditis, especially at the aortic site.[1] Although our findings indicate that annulus infection and abscess formation are common, ring abscess was not an absolute feature even of longstanding prosthetic infection leading to death. Half of our patients did *not* have ring infection at the time of autopsy. In only four cases were ring abscesses grossly apparent and in only three of the 11 (27 per cent) patients with ring abscesses did the abscess extend into the underlying myocardium and conducting system. Furthermore, active infection had been eradicated in four of our patients with prosthetic endocarditis treated with antibiotics, consistent with some recent reports of successful treatment of prosthetic valve endocarditis with antibiotics alone. Thus our results are considerably more

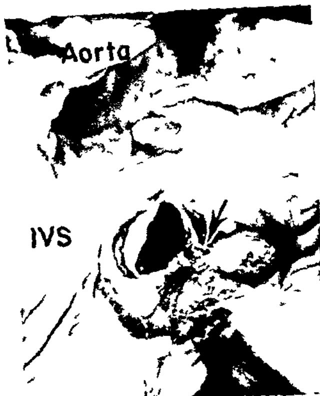


Fig 8 Mitral regurgitation caused by prosthetic endocarditis. The mitral homograft valve viewed from the left ventricle became incompetent from cusp destruction and fusion of a commissure *(arrow)*. *IVS* = interventricular septum.

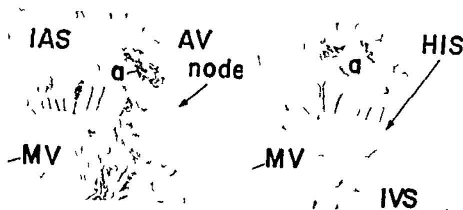


Fig. 5. First degree heart block caused by extension of an aortic valve ring abscess into the region of the atrioventricular (AV) node. *Left.* Histologic section showing the AV node partially destroyed by the abscess *(a)*. *Right.* A more anterior section shows an intact His bundle and a large abscess above it in the interatrial septum *(IAS)*. *MV* = mitral valve; *IVS* = interventricular septum. (Both Hematoxylin and eosin, × ›)



Fig. 6. Mitral valve prosthetic endocarditis causing mitral stenosis. Infected thrombus partially covers the left atrial *(LA)* aspect of the mitral prosthesis *(above)* and also extends into the struts of the cage within the left ventricle *(LV)* seen *below*. *PA* = pulmonary artery; *TV* = tricuspid valve; *RV* = right ventricle.

absence of the factors that mask the disease common in the early postoperative patient. Staphylococcus accounted for a third of the infecting organisms in this group of patients and, characteristically, these patients did not give a history of any invasive procedure commonly associated with a transient bacteremia.

Prosthetic infection is usually associated with dysfunction of the implanted valve[1] and occurred in over two thirds of our patients. Aortic valve endocarditis was characterized by annulus infection, dehiscence, cusp destruction, and secondary aortic incompetence. Large vegetations alone caused incompetence in two cases and stenosis in one. Mitral valve endocarditis was characterized by extensive vegetations causing mitral stenosis. Annulus infection was a less common finding in this location. Although the patterns of dysfunction differed between patients with aortic and those with mitral prostheses, in both groups the congestive heart failure that resulted from valve dysfunction was the leading cause of death.

As recognized by others,[1] emboli were a common finding in these patients both clinically and at autopsy, present in over 90 per cent of them, and were a significant cause of morbidity and mortality. The development of atrioventricular conduction block was also a clinical manifestation of aortic prosthetic endocarditis. In 21 per cent of our patients with aortic endocarditis, ring abscess extended into the conduction system and caused heart block. Of note, however, is that in two additional patients who developed left bundle branch block postoperatively, prior to the clinical presentation of their endocarditis, the bundle branch block was due to idiopathic

Retrograde left atrial catheterization in children with congenital heart disease

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Entry into the left atrium during cardiac catheterization is essential in some patients for the accurate measurement of pulmonary blood flow and pulmonary vascular resistance for the measurement of a mitral valve gradient or premitral obstruction. The majority of infants and children with congenital heart disease have a patent foramen ovale or atrial septal defect, thus making entry to the left atrium from the right relatively straightforward. In the remaining patients an alternative route must be used. Needle puncture of the left atrium, either percutaneously (direct or via the left ventricle) or by the transbronchial approach, is not suitable for use in children. Transseptal puncture through a closed fossa ovalis is less hazardous but there are few reports of the use of this technique in children. Entry into the left atrium during retrograde transaortic left heart catheterization in children was reported by Vlad and colleagues. Shirey and Sones described a tapered catheter specifically designed for retrograde left atrial catheterization primarily in adults and our experience since then has permitted us to assess objectively for the first time (as far as we are aware) the reliability and hazards of the method in children.

Material and methods

Over the past five years 1,300 cardiac catheterizations have been performed in this laboratory in patients with congenital heart disease. Retrograde catheterization of the left atrium was attempted only if attempts to cross a foramen ovale had failed and it was felt that entry to the left atrium would provide information essential for the management of the individual patient. It was therefore only attempted in 39 patients (3.1 per cent of all catheterizations). Each time a retrograde catheterization was attempted a careful note was made of the procedure, indications, and complications. Thus a simple prospective study was set up.

The Shirey catheter was used as the method of first choice for this purpose. In several patients, however, other catheters which were already in the left (pulmonary venous) ventricle for other reasons were successfully manipulated into the left atrium.

A right axillary arteriotomy was performed under local anaesthesia after whole body heparinization (100 units/Kg of body weight). The catheter was advanced to the ascending aorta and across the aortic valve either directly or by forming a catheter loop. In patients with complete transposition and ventricular septal defect (V.S.D.) or double outlet right ventricle the catheter was then passed across the V.S.D. Once the catheter tip was in the pulmonary venous ventricle, a loop was made and by careful rotation of the loop the catheter tip was placed posteriorly and advanced through the left atrioventricular (A/V) valve. Catheter tip pressure was monitored continuously and entry into the left atrium was signalled by a sudden drop in pressure in a zone of high oxygen saturation. In three of our patients a common ventricle was entered transvenously rather than transarterially, but essentially the same technique was used to enter the left atrium.

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optimistic with regard to antibiotic and surgical therapy than those reported by Arnett and Roberts who found ring abscess in all 18 of their autopsied patients with prosthetic endocarditis and suggested that antibiotics are incapable of eradicating infection One possible explanation for the differences between the two studies is that our series is composed of a non selected, consecutive group of autopsied patients from a single institution rather than a series of selected cases from several institutions It is possible that in the latter the selection process might introduce a bias towards more advanced and grossly apparent disease

In addition to the presence or absence of ring abscess the patient s cardiac status is another major factor in outcome of reoperation for prosthetic endocarditis Of the five patients in this study undergoing replacement of their infected valve four were in severe congestive heart failure prior to surgery and died either during the operation or shortly thereafter Thus to be effective surgical intervention should occur early before ring infection and intractable heart failure have developed Recognition of prosthetic dysfunction however is not always easy A new or changing murmur is a major indication of valve dysfunction but significant valve lesions were found at autopsy in patients without a clinical history of new murmurs Unfortunately the development of the signs and symptoms of congestive heart failure in patients not previously in failure or the sudden deterioration of a patient already in some degree of failure were the most common manifestation of prosthetic dysfunction Thus although it is sometimes possible to control prosthetic valve endocarditis with antibiotic therapy alone valve damage and vegetations remain despite successful eradication of the offending organism, and the residual prosthetic dysfunction most often requires surgical intervention

Summary

Although endocarditis is a frequently lethal complication of prosthetic valve replacement there is little pathological information on which to base diagnosis and treatment We have studied the clinical and pathological features of 22 patients with prosthetic valve endocarditis seen at The Johns Hopkins Hospital over the past 17 years Five patients developed endocarditis within two months of operation and 17 between two and 48 months (average 12) after operation Patients dying early had a more fulminant course and their endocarditis was less often recognized during life Late deaths tending to present with fever and bacteremia unmasked by postoperative problems were more readily recognized Mitral and aortic prosthetic endocarditis generally led to a different type of prosthetic valve dysfunction nine of 14 aortic valve prostheses with endocarditis developed incompetence and one other stenosis, five of seven patients with mitral valve prostheses developed stenosis and one a homograft developed incompetence Prosthetic valve dysfunction led to death in 10 patients (45 per cent) and embolic events in five (23 per cent) including four cerebrovascular accidents Ring infection often believed to be universally present and a contraindication to surgery was found only in 50 per cent of these patients In four patients (18 per cent) the endocarditis was sterilized by antibiotics but death occurred from valve dysfunction or emboli These findings suggest that early surgical intervention combined with antibiotics has a chance of providing effective therapy for prosthetic valve endocarditis

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ture[1] [1] In our hands closure of the axillary arteriotomy is followed by diminished or absent distal arterial pul ation in about ten per cent of cases over all This occurs most often in small infants and is unusual in children of the size de cribed in this paper In no case has ab ence of the distal arterial pulse been accompanied by symptoms or evidence of retarded growth of the limb Retrograde left atrial catheterization appears therefore to be a useful alternative to transseptal puncture particularly in smaller chil dren Because the retrograde approach is also of value in entering the pulmonary artery in complete transposition with ventricular septal defect and single primitive ventricle there need be no shortage of opportunities for perfect ing the delicate intraventricular manipulation required

Summary

Entry into the left atrium during cardiac cath eterization may be essential for full asses ment of the hemodynamic situation particularly for the accurate calculation of pulmonary blood flow and pulmonary arteriolar resistance The retrograde transaortic transmitral technique of left atrial catheterization has been described in adults but no detailed reports are available for the pediatric age group Experience of this technique in 43 children with congenital heart disease is now presented with a success rate of 67 per cent and a low incidence of complications This method compares favorably with other methods of left atrial catheterization when the interatrial sep tum is intact

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Table I Retrograde catheterization of the left atrium

	NCGA		Discordant (corrected) TGA		Concordant (complete) TGA with VSD	Single (Primitive) ventricle	Total
	Intact IVS	VSD	Intact IVS	VSD			
Successful	3	14	1	1	4†	7	30
Unsuccessful	1	6	0	0	3	3	13

Abbreviations NCGA = normally connected great arteries TGA = transposition of great arteries IVS = inter ventricular septum VSD = ventricular septal defect
Includes one patient with double outlet right ventricle and 1 malposition
†Includes one patient with persistent truncus arteriosus

Results

Deliberate attempts to enter the left atrium retrogradely were made in 39 patients with success in 26 (67 per cent) Unintentional entry occurred on 4 other occasions making a total of 30 retrograde left atrial catheterizations in all In 80 per cent of patients the indication for attempted left atrial catheterization was the suspected presence of severe pulmonary vascular disease All patients were aged 15 years or less The median weight of patients in whom the left atrium was entered was 17 0 Kg (range 5 4 to 42 Kg) compared with 13 7 Kg (range 7 1 to 32 Kg) in the unsuccessful group This difference is not statistically significant

The catheters used successfully to enter the left atrium retrogradely were Shirey (×17) NIH (×10) Sones Positrol (×3) Catheters which failed to enter the left atrium were Shirey (×11) NIH (×7) Sones Positrol (×3) Goodale Lubin (×1) and Eppendorf (×1) On only one occasion did a different type of catheter enter the left atrium retrogradely after a Shirey had failed to do so

Table I shows the basic diagnoses of the patients involved Left A/V valve abnormalities were present in 13 patients with stenosis present in four (successful left atrial catheterization in 1) and regurgitation in seven (successful left atrial catheterization in six)

In the first patient in whom the technique was tried sudden severe bradycardia occurred during manipulation in the left ventricle followed by ventricular fibrillation and although DC shock restored normal rhythm she died four hours later There was no evidence of cardiac trauma at autopsy which confirmed the catheterization diagnosis of persistent truncus arteriosus inoperable because of severe pulmonary vascular disease Subsequently manipulation was carried out with much greater caution and although short runs of premature ventricular contractions were invariably produced no other serious complications resulted On no occasion has it been necessary to administer atropine for a bradycardia

Discussion

Retrograde left atrial catheterization is indicated when simpler means of entering the left atrium have failed and it is essential to know accurately both the pulmonary venous oxygen saturation for determination of pulmonary blood flow by the Fick method in the presence of a right to left shunt and the left atrial pressure for the determination of the pulmonary arteriolar resistance This is particularly important in the presence of pulmonary vascular disease when the capillary wedge pressure may be unreliable

There are several factors which might determine the ease of retrograde left atrial catheterization Origin of the aorta from sites other than the left ventricle complicates the procedure but does not lessen the chance of success The smaller size of the infant heart does not seem to make manipulation more difficult but left A/V valve stenosis may lessen the likelihood of success

The best available alternative to retrograde left atrial catheterization is transseptal puncture which has been used in children with an 85 per cent incidence of success although the children reported in that study had weights significantly ($p < 0.001$) greater than those in this present study Our own experience confirms that retrograde left atrial catheterization is not without risk but then neither is transseptal punc

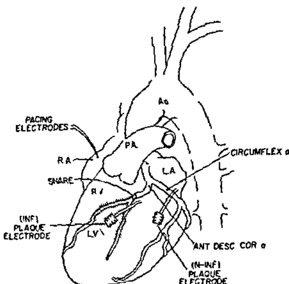


Fig 1 Schematic representation of the localization of the fibrillating plaque electrodes with a snare placed around the left anterior descending coronary artery Shaded area represents the infarct area (INF) and the other plaque electrode is placed in the non infarct area (N INF) A catheter is placed in the aorta (Ao) RA = right atrium LA = left atrium PA = pulmonary artery RV = right ventricle LV = left ventricle

Results

Control animals The stability of this preparation to repeated fibrillation threshold determinations was studied in three animals The VFT remained constant between 20 to 30 ma, averaging 26 ma during a six hour period

VFT prior to ligation Each dog served as his own control VFT determinations were obtained from the area to be infarcted (LAD) and the non infarcted area (circumflex) alternating between each area every 15 minutes Each control value prior to ligation was determined as the average value of at least three VFT determinations varying from one another by no more than 10 per cent The mean VFT for the entire group of 10 animals prior to coronary occlusion was 14 ma for the area supplied by the LAD and 17 ma for that supplied by the circumflex artery Table I shows the average of at least three VFT determinations for each dog expressed as actual measurements

VFT after ligation All the animals developed spontaneous ventricular premature contractions and six of the 10 had spontaneous ventricular fibrillation within 7 to 15 minutes following coronary ligation For animals fibrillating spontaneously the VFT was determined after a 15 minute interval following defibrillation

Table I Ventricular fibrillation threshold prior to coronary ligation

Animal	LAD*	CIR†
1	16	13
2	18	19
3	11	15
4	20	27
5	10	14
6	10	9
7	21	30
8	13	17
9	11	14
10	10	10
Mean	14 MA‡	1"6 MA

*LAD = area of the left anterior descending coronary artery
†CIR = area of the circumflex coronary artery
‡MA = milliamperes.

Fig 2 illustrates the time course of VFT following coronary ligation Within 15 to 30 minutes following ligation the mean of the infarcted area decreased to 11 ma and to 11 6 ma for the non infarcted area ($p < 0.025$) In both areas the VFT fell below the control values during the first 15 minutes after the ligation However within 90 to 120 minutes following coronary ligation VFT in the infarcted area (27 ma $p < 0.001$) was significantly higher than the control value The VFT continued to rise in the infarct area and at six hours the mean VFT was 50 6 ma ($p < 0.005$) In the non infarcted area VFT following coronary occlusion was low and remained below or near control VFT values during the entire course of the experiment

Threshold for a single response In order to explain the change in the VFT between the two areas we determined the minimal current required to produce a single response (i e excitability) in these areas in four dogs This was measured using the same plaque electrodes that were used for determining VFT Excitability is said to be decreased when a higher current strength is needed to stimulate the area Fig 3 represents the actual change in excitability of the two areas following coronary ligation In the non infarcted area a single response was always obtained with a current strength of 1 ma prior to and after coronary ligation However in the infarcted area the amount of current needed to elicit a single response increased with time follow

Time course of ventricular fibrillation threshold in infarcted and non-infarcted myocardium after acute coronary ligation

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After an acute myocardial infarction the myocardium becomes electrically unstable and spontaneous arrhythmias are frequent especially in the early stages[1,2] The infarcted ventricle is increasingly vulnerable to ventricular fibrillation during this early phase as evidenced by a decrease in the ventricular fibrillation threshold (VFT) However the time course of a reduced VFT following infarction has not been well documented This paper reports the time course of the VFT following acute coronary occlusion in the infarcted area and compares it to a non infarcted area of the left ventricle

Method

Mongrel dogs weighing 20 to 36 kilograms were anesthetized with intravenous sodium pentobarbital (30 mg /Kg) Respiration was maintained with the use of a Harvard respirator The heart was exposed through a left lateral thoracotomy and heart rate kept constant by crushing the sinus node and pacing the atria with bipolar plunge electrodes at a constant cycle length of 400 msec (150 beats per minute) The fibrillating current was delivered through bipolar platinum plaque electrodes with an inter electrode distance of 5 5 mm sutured with 5 0 silk to the epicardial surface of the left ventricle One bipolar plaque was placed in the area supplied by the left anterior descending coronary artery (LAD) and another on a remote area of the left ventricle supplied by the circumflex coronary artery A ligature was placed around the LAD approximately 2 cm from its origin (Fig 1)

The fibrillating pulse train had a duration of 200 msec and consisted of 20 pulses each 2 msec in width and 8 msec apart The train was delivered 50 msec after the last paced QRS complex thereby ensuring its delivery during the ventricular vulnerable period Following delivery of the pulse train pacing was discontinued for one basic cycle length to avoid competition between induced ventricular beats and atrial paced beats The pulse train was delivered after every fifteenth paced beat and had a constant current source The strength of the train was increased by one milliampere (ma) increments until ventricular fibrillation occurred VFT was defined as the least amount of current required to produce ventricular fibrillation The current delivered was measured directly by recording the voltage drop across a precision 1 kohm resistor in series with the electrodes The heart was then defibrillated within 10 seconds with low current DC counter shock A 15 minute recovery period was permitted between consecutive VFT determinations Continuous arterial pressures were recorded by means of a catheter placed in the femoral artery Arterial blood gases were monitored periodically and maintained within a narrow physiologic range The temperature of the animal was recorded using a rectal probe

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the electrical response of ischemic myocardium with monopolar bipolar cathodal and anodal stimulation They found that the infarcted tissue became less excitable to bipolar stimulation within less than one hour after coronary ligation However a response was obtained if sufficient strength was used Immediately following coronary occlusion there was a decrease in the diastolic threshold followed by a gradual rise in the threshold as the tissue became less excitable

An alternative explanation for the rise in VFT in the infarcted area is improvement of blood supply to the area Measurements of regional myocardial blood flow by radioactive microsphere techniques have shown that following coronary occlusion there is a redistribution of blood flow to the infarcted area through the development of collateral circulation Dixon and co workers have shown that VFT correlates well with the blood supply in the infarcted area in dogs Graded reduction in perfusion of the coronary artery was associated with a fall in VFT Conversely MacLean and Phibbs[3] have shown that the decrease in VFT during reduction in perfusion can be prevented by a revascularization procedure These experiments suggest that redistribution of blood flow in an infarcted area can bring the VFT to normal

If collateral circulation had been the reason for increase in VFT in the present study excitability should also have been normal Our study clearly documented a decrease in excitability suggesting that the increase in VFT was due to changes in the infarcted tissue itself rather than to altered blood supply Furthermore although collateral flow may increase to an infarcted area after coronary occlusion the time course of the increase in flow is much slower than the observed course of VFT in our study

VFT has been extensively used to study the effect of various interventions in the normal and ischemic myocardium Our study suggests that the localization of the electrode used for fibrillation and the time course of the VFT are essential in evaluating VFT in the ischemic myocardium As shown in the present study if the fibrillating electrodes are in the infarcted area the VFT tends to increase with time This natural rise in VFT may be misinterpreted as a beneficial effect of an intervention that is used in acute ischemia In addition the increase in VFT and altered excitability within the infarcted area may support the concept that the infarcted i e dead tissue is not the site of arrhythmias that occur after infarction [*] On the other hand the subendocardial[1] or border area may play a significant role in the genesis of lethal arrhythmias

Summary

The time course of the ventricular fibrillation threshhold (VFT) was studied in 10 open chest mongrel dogs following acute occlusion of the left anterior descending coronary artery (LAD) The VFT in the infarcted area was compared to a non infarcted area of the left ventricle supplied by the circumflex coronary artery Prior to coronary occlusion the mean VFT for the entire group of 10 animals was 14 ma for the area supplied by the LAD and 17 6 ma for the area of the left circumflex Immediately after coronary ligation the VFT decreased in both areas Within 90 to 120 minutes the VFT in the infarcted area was 27 ma and after 6 hours of occlusion the VFT was 3 times the pre ligation value The VFT in the non infarcted area remained near the pre ligation values The excitability of the infarcted area was markedly decreased after coronary occlusion and this accounted for the increase in the VFT in the infarcted area In the non ischemic area the excitability was unchanged during the entire six hour period following occlusion The study stresses the importance of the location of the electrodes used for fibrillation and the natural course of the VFT in evaluating VFT s within the ischemic myocardium

The authors wish to express their thanks to Horace Brown and Evelyn Chute for their technical and editorial assistance in this study

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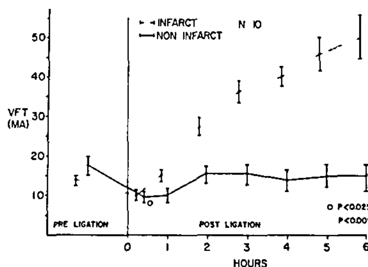


Fig 2 Time course of the VFT prior to and after coronary ligation for the entire group of 10 animals On the vertical axis is the VFT in milliamperes (*MA*) and on the horizontal axis is the time in hours Time 0 represents the time of recovery ligation The solid line depicts the non infarct area and the broken line the infarct area Each point is expressed as the mean ± 2 standard errors

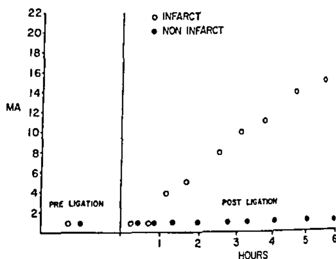


Fig 3 Time course of the threshold for a single response prior to and after coronary ligation On the vertical axis is the current strength in milliamperes (*MA*) and on the horizontal axis is the time in hours Closed circles represent the non infarct area and open circles the infarct area

ing coronary ligation The infarcted area became less responsive to electrical stimulation This may explain the rise in VFT in the infarcted area

Discussion

In the 1940s Wiggers and associates scanned the vulnerable period of the ventricle using a 10 msec pulse and found they could initiate ventricular fibrillation by increasing the current strength of the pulse They defined VFT as the lowest amount of energy required to produce ventricular fibrillation However this method is time consuming and may not be suitable for the study of the time course of VFT Han modified this technique by using a train of pulses to cover the vulnerable period gradually increasing the strength of the train until ventricular fibrillation occurred This method allows determination of a series of VFTs in a short period of time and was therefore chosen as the method used in the present study

Following myocardial infarction the ventricle becomes electrically unstable and the VFT is low[3] Han first demonstrated that with myocardial ischemia there is an increase in the degree of temporal dispersion of the recovery of the ventricle Ischemia results in non homogeneity of conduction velocities and refractory periods between adjacent cells This asynchrony between the cells is an ideal situation for the initiation of re entry which may then result in premature ventricular beats and ventricular fibrillation Recent studies by El Sheriff and colleagues have shown that the mechanism of ventricular fibrillation in acute ischemia is a delayed conduction through the infarcted area and compatible with re entry

The time course of vulnerability to fibrillation after experimental coronary ischemia has been studied by Burgess and colleagues They found that five minutes after coronary occlusion there is a significant increase in the vulnerability to fibrillation (decrease in the VFT) and that after 30 minutes the vulnerability has returned to control values They placed electrodes on the right ventricle or in a non infarcted area and their findings are therefore comparable to our non infarcted area

In contrast to the non infarcted area the VFT in the infarcted area initially decreased and then started to rise 90 minutes after the occlusion Six hours after occlusion the VFT in the infarcted area was three times that of the control value To explain this phenomenon we studied the excitability of the infarcted area during this time period Before coronary artery ligation excitability was the same in the two areas after ligation as VFT increased excitability decreased in the infarcted area The decrease in excitability was parallel to the increase in VFT These results demonstrate that more current is necessary to elicit a response in the infarcted tissue thus increasing VFT

Brooks and associates[1] studied excitability and

Electrophysiologic properties of nitroglycerin in man

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There is considerable interest in selecting the proper drug to preserve the ischemic myocardium or twilight zone in a patient with a recent myocardial infarction Vasodilator therapy with an infusion of nitroprusside[1] or phentolamine has been shown to improve left ventricular function by a reduction of both preload and afterload Sublingual nitroglycerin as well as an infusion of nitroglycerin can also alleviate left ventricular failure in patients with an acute myocardial infarction Further precordial mapping studies have shown that nitroglycerin can decrease the sum of the ST segment elevations in patients with an acute myocardial infarction This suggests that nitroglycerin not only improves left ventricular function but also decreases the extent of myocardial ischemia

Recently nitroglycerin has been shown to increase the threshold at which ventricular fibrillation could be induced electrically during experimental coronary occlusion The drug can also inhibit the spontaneous occurrence of ventricular fibrillation during acute coronary occlusion in dogs Preliminary data have been presented suggesting that nitroglycerin administered sublingually to patients with an acute myocardial infarction decreases the number of ventricular premature beats occurring during the first 24 hours after admission to the coronary care unit

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The present study involving 13 human subjects was undertaken to determine what effects sublingually administered nitroglycerin has on refractoriness of the atrium A V node and His Purkinje system at paced cycle lengths Measurements were also made of A V nodal and His Purkinje conduction time over a range of paced atrial rates This information is not available for such a widely used drug

Material and methods

The study group consisted of 13 patients with organic heart disease The clinical features of the group are summarized in Table I All patients were informed of the nature of the study and gave informed consent They were studied in the supine position in a postabsorptive nonsedated state

Under local anesthesia a quadripolar electrode catheter was introduced percutaneously into the right antecubital vein and fluoroscopically positioned against the lateral wall of the high right atrium near its junction with the superior vena cava The distal pair of electrodes was used to stimulate the atrium while the proximal pair was used to record a high right atrial electrogram In addition a bipolar pacing catheter was introduced percutaneously into the right femoral vein and fluoroscopically positioned at the tricuspid valve The position was adjusted to obtain optimal recordings of the bundle of His electrogram The proximal terminals of the catheter were attached to an electrocardiographic amplifier and the bipolar His electrogram was recorded at a frequency setting of 40 to 500 cycles/sec on a DP 12 Electronics for Medicine recorder at paper

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Electrophysiologic properties of nitroglycerin in man

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There is considerable interest in selecting the proper drug to preserve the ischemic myocardium or twilight zone in a patient with a recent myocardial infarction. Vasodilator therapy with an infusion of nitroprusside or phentolamine has been shown to improve left ventricular function by a reduction of both preload and afterload. Sublingual nitroglycerin as well as an infusion of nitroglycerin can also alleviate left ventricular failure in patients with an acute myocardial infarction. Further, precordial mapping studies have shown that nitroglycerin can decrease the sum of the ST segment elevations in patients with an acute myocardial infarction. This suggests that nitroglycerin not only improves left ventricular function but also decreases the extent of myocardial ischemia.

Recently, nitroglycerin has been shown to increase the threshold at which ventricular fibrillation could be induced electrically during experimental coronary occlusion. The drug can also inhibit the spontaneous occurrence of ventricular fibrillation during acute coronary occlusion in dogs. Preliminary data have been presented suggesting that nitroglycerin administered sublingually to patients with an acute myocardial infarction decreases the number of ventricular premature beats occurring during the first 24 hours after admission to the coronary care unit.

The present study, involving 13 human subjects, was undertaken to determine what effects sublingually administered nitroglycerin has on refractoriness of the atrium, A-V node, and His-Purkinje system at paced cycle lengths. Measurements were also made of A-V nodal and His-Purkinje conduction time over a range of paced atrial rates. This information is not available for such a widely used drug.

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Table III Effects of nitroglycerin on refractory periods of the A V conducting system

Patient no	Paced cycle length (msec)	ERP of atrium (msec)		ERP of AV node (msec)		FRP of AV node (msec)		RRP of HPS (msec)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	5 0	280	265		—	300	360	—	—
2	600	245	230	300	275	400	360	—	—
3	570	210	200	355	285	415	340	—	—
4	570	240	200		—	360	340	400	380
5	600	2 5	260	390	300	400	380	440	400
6	600	300	285		—	380	360	400	360
7	600	300	80	355	340	460	410	—	—
8	600	3 5	290		—	430	400	—	—
9	857	370	290	685	59	60	430	—	—
10	600	235	235		—	470	380	470	370
11	40	—	—	635	600	40	680	—	—
12	600	290	230		—	400	390	—	—
13	600	90	260		—	430	400	480	430
Mean ± S E M		280 ± 12 Pre 259 ± 9 Post		442 ± 70 Pre 401 ± 63 Post		460 ± 38 Pre 429 ± 35 Post		428 ± 15 Pre 39 ± 16 Post	
P value		<0 01		<0 0		<0 001		<0 01	

Electrophysiologic studies limited due to atrial refractoriness.

sinus node pacemaker after sudden cessation of the highest pacing rate obtained was observed before and after the drug

The following definitions were used in regard to refractory periods A H and V were the atrial His bundle and ventricular electrograms of driven beats (S_1) A_2 H_2 and V_2 were the atrial His bundle and ventricular electrograms in response to the *extrastimulus* (S_2) The atrial effective refractory period was the longest S_1 S_2 interval at which S_2 did not result in atrial depolarization The A V nodal *effective* refactory period was the longest A_1 A_2 interval at which A_2 failed to conduct to the *bundle of His* The A V nodal functional refractory period was the shortest interval between H_1 H_2 both of which were propagated from the atrium The relative refractory period of the His Purkinje system was the longest H_1 H_2 at which H_2 *conducted to the* ventricles with a longer HV interval than that of the basic drive beat or with a QRS with aberrant configu*ration*

Nitroglycerin 1/150 grain was then administered sublingually to each *patient after* control recordings When the sublingual tablet completely disappeared the electrophysiologic studies were repeated The blood pressure was also obtained with a sphygmomanometer before and after the administration of the sublingual *nitroglycerin* The disappearance of the sublingual tablet was used as the end point *Statistical analysis of all* data was performed using the Student t test *for* paired data

Results

The effects of *nitroglycerin on the conduction* system are presented in Tables II and III

Intraatrial conduction The P A interval was measured in all patients The *mean* P A interval ± standard error of the mean was 32 ± 3 before and after nitroglycerin administration The atrial effective refractory periods could be measured in 12 patients The *mean effective* refractory period of the atrium was 260 ± 12 msec before and 259 ± 9 msec after nitroglycerin *administration* ($p < 0.01$)

A V nodal conduction A H intervals could be measured in all patients The mean A H interval during sinus rhythm was 112 ± 15 msec before and 103 ± 14 msec after administration of nitroglycerin With atrial pacing A H intervals at equivalent paced rates (100 to 140/min) were significantly different before *and after nitroglyc*erin For example the mean A H interval at a paced rate of 100/min in 8 patients was 113 ± 8 msec *before* and 99 ± 10 msec after nitroglycerin ($p < 0.01$) At a pacing rate of 120/min the A H interval was 124 ± 8 *msec* before and 111 ± 9 msec after nitroglycerin ($p < 0.01$) While at a pacing rate of 140/min the control A H interval

Table I Clinical data

Patient number	Age (yr)	Sex	Diagnosis	Electrocardiographic findings
1	51	M	Arteriosclerotic heart disease	Complete left bundle branch block
2	64	M	Arteriosclerotic heart disease	Complete left bundle branch block
3	65	M	Arteriosclerotic heart disease	Complete right bundle branch block left ant hemiblock old inf M I
4	73	F	Arteriosclerotic heart disease	Old antero septal M I Left ventricular hypertrophy
5	68	M	Syncope—etiology unknown	First degree A V block—nonspecific ST T wave changes
6	59	M	Arterio sclerotic heart disease	Sinus bradycardia old inferior wall myocardial infarction
7	71	F	Sick sinus syndrome	Sinus bradycardia periods of sinus arrest and atrial flutter
8	81	F	Episodes of supraventricular tachycardias	Left ventricular hypertrophy
9	76	M	Sick sinus syndrome	Sinus bradycardia first degree A V block
10	54	M	Arteriosclerotic heart disease	Old antero septal myocardial infarction
11	75	M	Arteriosclerotic heart disease	First degree A V block nonspecific ST T wave changes
12	48	M	Syncope etiology unknown	Sinus bradycardia
13	88	M	Sick sinus syndrome	Sinus bradycardia sinus arrests junctional rhythm

Table II Summary of atrioventricular and intraventricular conduction (in msec) in 13 patients before and after nitroglycerin administration

	No of patients	State	Mean ± SEM	P value
Sinus rate (beats/min)	13	C	70 ± 6	<0 001
		N	83 ± 7	
Blood pressure (mm Hg)	13	C	133/78 ± 3/3	<0 001
		N	119/70 ± 4/2	
P A interval	13	C	32 ± 3	N S
		N	32 ± 3	
A H interval	13	C	112 ± 15	<0 001
		N	103 ± 14	
H V interval	13	C	44 ± 3	N S
		N	44 ± 3	
A H interval (at HR 100/min)	8	C	113 ± 8	<0 01
		N	99 ± 10	
A H interval (at HR 120/min)	10	C	124 ± 8	<0 01
		N	111 ± 9	
A H interval (at HR 140/min)	11	C	150 ± 14	<0 02
		N	130 ± 10	
Sinus nodal recovery time	11	C	1097 ± 184	N S
		N	847 ± 80	
Heart rate during Wenckebach periods (beats/min)	9	C	143 ± 11	<0 02
		N	157 ± 11	

HR = heart rate N S = not significant C = control N = nitroglycerin

speeds of 100 mm/sec Simultaneous electrocardiographic Leads I II and III were recorded

Conduction studies were carried out during sinus rhythm and at various paced atrial rates up to a maximum of 190 beats/minute Atrial stimulation was performed using a programmed digital stimulator that delivered impulses of 1 5 msec duration at approximately twice diastolic threshold

The refractory periods of the atrium A V node and His Purkinje system were determined by the extrastimulus method A cycle length approximately 20 per cent faster than the sinus rate was utilized so that refractory periods could be measured at identical cycle lengths before and after administration of nitroglycerin The following intervals were measured in milliseconds

1 *The P A interval* The interval from the onset of the P wave during normal sinus conduction recorded on the standard electrocardiographic lead to the first rapid deflection of the A wave on the bipolar electrogram The P A time represents intraatrial conduction time The normal value is 27 ± 18 msec[11] During atrial pacing the P A time is measured from the pacing impulse to A

2 *A H interval* The interval from the first rapid deflection of the A wave to the first rapid deflection of the bundle of His electrogram The A H time represents conduction time through the A V node The normal value is 92 ± 38 msec[1]

3 *H V interval* The interval from the first rapid bundle of His deflection to the onset of the QRS deflection in the electrocardiogram The H V interval approximates conduction time in the specialized tissues of the His Purkinje system The normal value is 43 ± 12 msec[1]

For each of these intervals 10 beats were averaged before and after the administration of nitroglycerin and the mean values were used for comparison In addition the recovery time of the

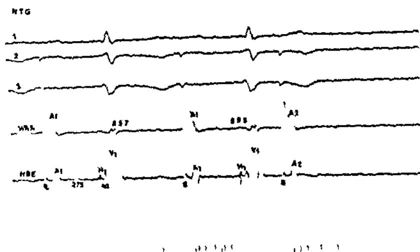


Fig 1C In this tracing block of A above the His bundle occurs and the effective refractory period of the AV node is reached. Thus nitroglycerin shortened the effective refractory period of the AV node by 100 msec For explanation see *Fig 1A*

were not changed in any patient by the administration of nitroglycerin The relative refractory period of the His Purkinje system could be measured in 5 patients The mean values were respectively 428 ± 15 msec before and 392 ± 16 msec after nitroglycerin ($p < 0.01$) (Fig 2)

Automaticity and recovery periods of the sinus node The sinus rate increased in all patients The mean sinus rate was 70 ± 6 beats/min before and 83 ± 7 beats/min after nitroglycerin ($p < 0.001$) Sinus node recovery times decreased after nitroglycerin Mean recovery times before and after nitroglycerin were 1097 ± 184 msec and 847 ± 80 msec respectively (N S)

Blood pressure The blood pressure fell in every patient after nitroglycerin administration The mean values were respectively 133/78 ± 3/3 mm Hg before and 119/70 ± 4/2 mm Hg after nitroglycerin ($p < 0.001$)

Discussion

The present study revealed that nitroglycerin administration produced a significant reduction in the A H interval in the control state as well as at the various atrial pacing rates In a previous report from this laboratory nitroglycerin was found to consistently enhance A V nodal conduction in man [1] Consistent with these finding is the fact that in every patient the functional refractory period of the A V node decreased Further the effective refractory period of the A V node also shortened in every patient in whom this interval could be measured Nitroglycerin did not affect His Purkinje conduction time (H V interval) during sinus rhythm and over a wide range of paced atrial rates However the relative refractory period of the His Purkinje system was decreased in the 5 patients who were also to have this measurement performed The P A interval a measure of conduction from the high to low right atrium was unaltered after administration of nitroglycerin It is of interest that the effective refractory period of the atrium showed a small but significant decrease after nitroglycerin administration

The effects of nitroglycerin on the sinus node have been well studied in man It has been demonstrated that nitroglycerin has a positive chronotropic effect on the sinus node [12] The data from our study on enhanced automaticity are in agreement with previous observations The sinus rate increased in all patients after administration of nitroglycerin In addition nitroglycerin decreased the sinus nodal recovery time in every patient Further a significant decrease in the systemic blood pressure was observed in every patient

This improvement in conduction through the A V node can probably be explained by a secondary effect of nitroglycerin mediated

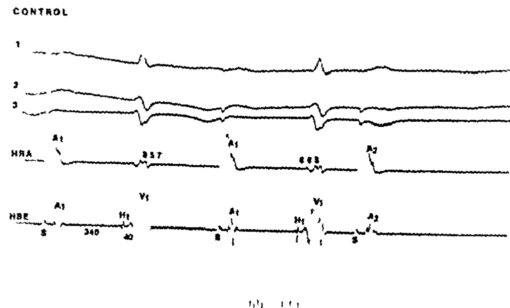


Fig 1A Effects of nitroglycerin on the effective refractory period of the A V node (patient No 9) *Figs 1A 1B* and *1C* are each organized as follows top to bottom standard Leads I II III high right atrial electrogram *(HRA)* His bundle electrogram *(HBE)* and time lines of 20 msec The basic paced atrial cycle length is 857 msec *A* Control panel the effective refractory period of the AV node is reached at an atrial coupling interval (A A) of 685 msec After the administration of nitroglycerin A continues to conduct to the His Purkinje system at an A A interval of 600 msec

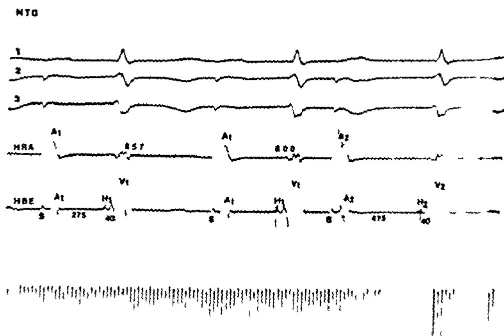


Fig 1B When the A A interval is decreased to 595 msec For explanation see *Fig 1A*

was 150 ± 14 msec and the post drug interval was 130 ± 10 msec ($p < 0.02$) The paced rate at which Wenckebach periods proximal to the His bundle occurred was noted in 9 patients This mean rate was 143 ± 11 beats/min before and 157 ± 11 beats/min after nitroglycerin ($p < 0.02$) The mean A V nodal functional refractory period was 460 ± 36 msec before and 429 ± 35 msec after nitroglycerin ($p < 0.001$) The effective refractory period of the A V node was 442 ± 70 msec before and 401 ± 63 msec after administration of nitroglycerin ($p < 0.05$) (Fig 1)

Intraventricular conduction The H V intervals

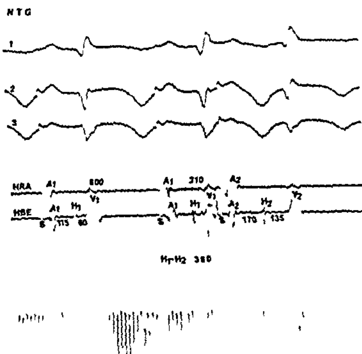


Fig 2B After the administration of nitroglycerin at an H H interval of 360 msec the QRS complex is aberrant and the H V has lengthened Therefore nitroglycerin produced a 40 msec decrease in the relative refractory period of the His Purkinje system For explanation see *Fig 2A*

sublingually for 24 hours to 23 patients with an acute myocardial infarction An additional 23 patients did not receive the drug A very significant decrease in the frequency of ventricular premature beats was seen in the group on nitroglycerin The heart rate in both groups was comparable but the mean blood pressure fell by 10 mm Hg in the treated group The authors postulated that perhaps the beneficial action of the drug was due to an improvement in the oxygen requirement blood flow ratio In our patients no new arrhythmias were noted after administration of nitroglycerin thus suggesting that nitroglycerin is not arrhythmogenic in man We cannot draw any conclusions about the antiarrhythmic properties of nitroglycerin from this study However the results indicate that the enhanced conduction through the A V transmission system possibly along with the increase rate effect would tend to diminish the occurrence of arrhythmias

Summary

His bundle electrograms were obtained in 13 patients before and after the sublingual administration of nitroglycerin The P A interval measured in all patients was 32 ± 3 msec (mean ± standard error of the mean) before and after nitroglycerin (N S) The mean A H interval during sinus rhythm in all patients was respectively 112 ± 15 msec before and 103 ± 14 after nitroglycerin ($p < 0.001$) The mean A H interval at a paced rate of 140/min in 11 patients was 150 ± 14 msec before and 130 ± 10 msec after nitroglycerin ($p < 0.02$) The mean H V interval was 44 ± 3 before and after nitroglycerin (N S) The mean sinus rate and sinus recovery times were respectively 70 ± 6 beats/min and 1097 ± 184 msec before and 83 ± 7 beats/min and 847 ± 80 msec after nitroglycerin ($p < 0.001$ and N S) The blood pressure fell in every patient after nitroglycerin The mean values were respectively 133/78 ± 3/3 mm Hg before and 119/70 ± 4/2 mm Hg after nitroglycerin ($p < 0.001$) Functional and effective refractory periods were measured (in milliseconds) with the use of the atrial extrastimulus technique The mean atrial effective refractory period (12 patients) were 280 ± 12 msec before and 259 ± 9 msec after

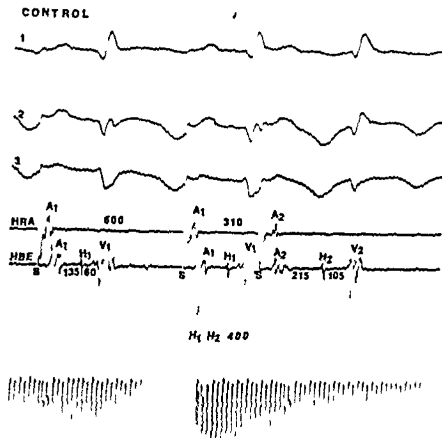


Fig 2A Effect of nitroglycerin on the relative refractory period of the His Purkinje system (patient No 6) The basic paced atrial cycle length is 600 msec A control panel A_2 is introduced at an atrial coupling cycle (A_1 A_2) of 310 msec The resulting QRS complex is aberrant and the H_2 V_2 interval lengthens The critical H_1 H_2 interval is 400 msec and defines the relative refractory period of the His Purkinje system during the control period

through the autonomic nervous system One of the major hemodynamic effects of nitroglycerin is systemic hypotension which reflexly will increase sympathetic drive to the heart and decrease vagal tone Similarly both the onset of second degree A V heart block at higher pacing rates and the reduction in the sinus node recovery time after nitroglycerin could be explained by a similar mechanism Similar studies under the influence of atropine and propranolol should be done to determine if nitroglycerin has any direct effect other than that which involves the reflex mechanism discussed

Recently Kent and co workers explored the possibility that the decrease in ischemia caused by nitroglycerin reduces the frequency of lethal arrhythmias These workers assessed the effects of nitroglycerin on ventricular fibrillation threshold an electrophysiologic index that correlates inversely with the tendency of the ventricle to fibrillate spontaneously Myocardial ischemia produced by occlusion of the left anterior descending coronary artery, markedly diminished the ventricular fibrillation threshold When nitroglycerin was infused intravenously during ischemia at a rate sufficient to decrease mean arterial pressure by an average of 19 mm Hg fibrillation threshold increased considerably When the same dose of nitroglycerin was accompanied by simultaneous administration of phenylephrine to avoid hypotension, the fibrillation threshold increased to the levels present in the absence of ischemia Thus nitroglycerin enhances electrical stability of the heart during experimental acute myocardial ischemia This beneficial electrophysiologic effect has also been shown to be associated with an actual decrease in the frequency of ventricular fibrillation during acute coronary occlusion in dogs Epstein and his group[11] concluded that nitroglycerin may be uniquely valuable in the treatment of acute myocardial infarction by reducing the degree of ischemic injury and the incidence of serious ventricular arrhythmias The mechanisms involved in the antiarrhythmic action of the drug were not elucidated by these workers

Recently Mihalick and associates administered 1/150 grain of nitroglycerin every four hours

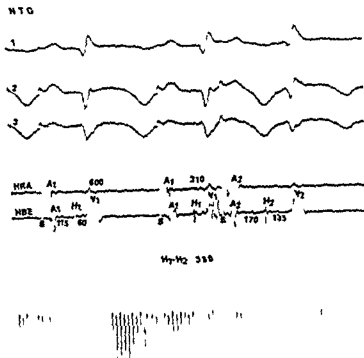


Fig 2B. After the administration of nitroglycerin at an H-H interval of 360 msec the QRS complex is aberrant and the H-V has lengthened. Therefore nitroglycerin produced a 40 msec decrease in the relative refractory period of the His-Purkinje system. For explanation see *Fig. 2A*.

sublingually for 24 hours to 23 patients with an acute myocardial infarction. An additional 23 patients did not receive the drug. A very significant decrease in the frequency of ventricular premature beats was seen in the group on nitroglycerin. The heart rate in both groups was comparable but the mean blood pressure fell by 10 mm Hg in the treated group. The authors postulated that perhaps the beneficial action of the drug was due to an improvement in the oxygen requirement blood flow ratio. In our patients no new arrhythmias were noted after administration of nitroglycerin, thus suggesting that nitroglycerin is not arrhythmogenic in man. We cannot draw any conclusions about the antiarrhythmic properties of nitroglycerin from this study. However, the results indicate that the enhanced conduction through the A-V transmission system possibly along with the increase rate effect would tend to diminish the occurrence of arrhythmias.

Summary

His bundle electrograms were obtained in 13 patients before and after the sublingual administration of nitroglycerin. The P-A interval measured in all patients was 32 ± 3 msec (mean ± standard error of the mean) before and after nitroglycerin (N.S.). The mean A-H interval during sinus rhythm in all patients was respectively 112 ± 15 msec before and 103 ± 14 after nitroglycerin ($p < 0.001$). The mean A-H interval at a paced rate of 140/min in 11 patients was 150 ± 14 msec before and 130 ± 10 msec after nitroglycerin ($p < 0.02$). The mean H-V interval was 44 ± 3 before and after nitroglycerin (N.S.). The mean sinus rate and sinus recovery times were respectively 70 ± 6 beats/min and 1097 ± 184 msec before and 83 ± 7 beats/min and 847 ± 80 msec after nitroglycerin ($p < 0.001$ and N.S.). The blood pressure fell in every patient after nitroglycerin. The mean values were respectively 133/78 ± 3/3 mm Hg before and 119/70 ± 4/2 mm Hg after nitroglycerin ($p < 0.001$). Functional and effective refractory periods were measured (in milliseconds) with the use of the atrial extrastimulus technique. The mean atrial effective refractory period (12 patients) were 280 ± 12 msec before and 259 ± 9 msec after

nitroglycerin ($p < 0.01$) The mean atrioventricular (A V) nodal functional refractory period (13 patients) and effective refractory period (6 patients) were 460 ± 36 and 442 ± 70 msec before and 429 ± 35 and 401 ± 63 msec after nitroglycerin ($p < 0.001$ and $p < 0.05$) The mean relative refractory period of the His Purkinje system (5 patients) was 428 ± 15 before and 392 ± 16 msec after nitroglycerin ($p < 0.01$)

In summary, nitroglycerin increased sinus nodal automaticity as manifested by an increase *in sinus rate and improved A V nodal conduction* as manifested by a reduction in the A H interval and the A V nodal functional and effective refractory periods This is probably explained by the systemic hypotension produced by nitroglycerin which reflexly will increase sympathetic drive to the heart and decrease vagal tone

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Echocardiographic features of combined membranous subaortic stenosis and acquired calcific aortic valvulopathy

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The combination of congenital fixed subaortic stenosis and acquired calcific aortic valvulopathy is an unusual cause of left ventricular outflow tract (LVOT) obstruction and aortic insufficiency in the middle aged adult We describe a 45 year old white male with both a congenital subaortic diaphragm and a probably acquired aortic valve deformity leading to the clinical diagnosis of calcific aortic valvular stenosis and insufficiency The abnormal structure and motion of the aortic valve on the M mode echocardiogram suggested both aortic valvular and subvalvular lesions prior to surgery

Case report

A C a 4 -year old white male was referred to Strong Memorial Hospital in January 1974 for evaluation of cardiac murmurs There was no history of rheumatic fever infective endocarditis or familial heart murmurs

Physical examination revealed a heart rate of 80 per minute and a blood pressure of 110/80 mm Hg The lungs were clear Cardiac examination demonstrated a localized sustained apical impulse in the normal position a normal first and second heart sound a Grade III/VI harsh crescendo-decrescendo systolic ejection murmur maximal at the apex with radiation to the entire precordium and both carotid arteries a Grade II/VI high pitched decrescendo early diastolic murmur maximal at the left sternal border normal carotid upstroke and normal jugular venous pulses

The electrocardiogram demonstrated left ventricular hypertrophy by precordial voltage criteria The chest x ray showed a normal cardiac silhouette with prominence of the ascending aorta

M mode cardiac ultrasonography was performed with a commercially available echograph (Picker) and a 2 25 mHz transducer focused at " cm Continuous records were made on a 35 mm film by means of a Fairchild oscilloscope record camera and a dual beam oscilloscope operating as a slave The echocardiogram (Fig 1) demonstrated a slightly enlarged aortic root (width = 40 mm) containing multiple central diastolic echoes consistent with a thickened, calcified tricuspid aortic valve Both the anterior (right coronary) and posterior (non-coronary) cusps showed rapid opening movements toward the periphery of the aortic root in systole The right coronary cusp immediately after opening executed an abrupt rapid movement toward closure and remained in the semi closed position for the remainder of systole a finding indicative of fixed subaortic left ventricular outflow tract obstruction Ultrasound beam scanning from the mitral valve to the aortic root failed to show either narrowing of the LVOT or linear echoes in the LVOT observed occasionally with subaortic membranes The mitral valve was structurally normal but demonstrated diastolic flutter of the anterior leaflet consistent with aortic insufficiency

Cardiac catheterization and angiography utilizing the transseptal approach demonstrated a peak systolic pressure gradient across the LVOT of 40 mm Hg with a left ventricular cavity pressure of 155/10 mm Hg and systemic artery pressure of 115/60 mm Hg a moderate amount of calcium in the area of a tricuspid aortic valve and moderate aortic insufficiency No definite subaortic diaphragm was demonstrated Coronary arteriograms were normal

Because his symptoms were not severe and since cardiac hemodynamics and angiography indicated a moderate degree of LVOT obstruction and aortic insufficiency surgery was deferred

The patient returned to Strong Memorial Hospital in January 19 6 with symptoms of moderate dyspnea on exertion and anterior chest heaviness consistent with angina pectoris Physical examination electrocardiogram chest x ray cardiac ultrasonography and repeat coronary arteriography were unchanged from the studies of 1974 Repeat cardiac catheterization was not performed In view of signifi

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Echocardiographic features of combined membranous subaortic stenosis and acquired calcific aortic valvulopathy

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The combination of congenital fixed subaortic stenosis and acquired calcific aortic valvulopathy is an unusual cause of left ventricular outflow tract (LVOT) obstruction and aortic insufficiency in the middle aged adult [1] [2] We describe a 45 year old white male with both a congenital subaortic diaphragm and a probably acquired aortic valve deformity leading to the clinical diagnosis of calcific aortic valvular stenosis and insufficiency The abnormal structure and motion of the aortic valve on the M mode echocardiogram suggested both aortic valvular and subvalvular lesions prior to surgery

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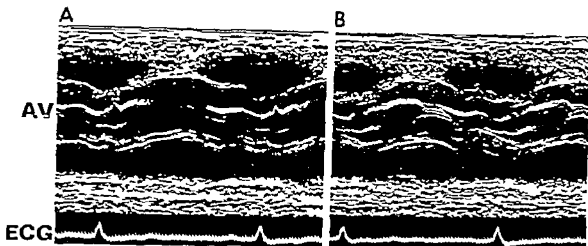


Fig 1 A and B *A* Aortic valve echocardiogram from patient A C demonstrating an early systolic rapid movement toward closure *of the anterior (right coronary) cusp suggesting a subaortic diaphragm B Aortic valve* echocardiogram from patient A C demonstrating multiple diastolic echoes consistent with aortic cusp thickening and calcification *AV* = aortic valve *ECG* = electrocardiogram

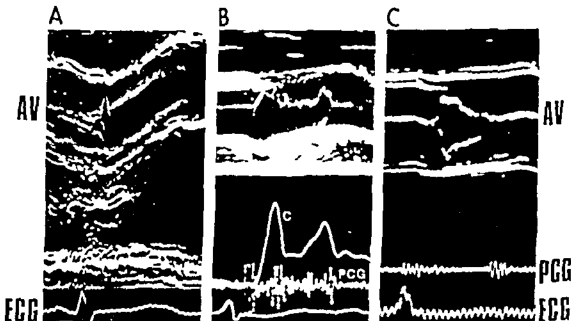


Fig 2 *A B* and *C A* Aortic valve echocardiogram *from a young girl with a subaortic membrane and normal* aortic valve demonstrating an early systolic rapid movement toward closure of the anterior (right coronary) cusp *B* (*top*) Aortic valve echocardiogram from a patient with hypertrophic obstructive cardiomyopathy (*HOCM*) showing early systolic gradual movement toward closure with maintenance of a semi closed position through midsystole and then a reopening movement in late systole of the anterior (right coronary) cusp *B* (*bottom*) *Simultaneous carotid pulse tracing and phonocardiogram C Aortic valve echocardiogram from a patient* with mitral regurgitation and reduced forward cardiac output showing gradual systolic movement toward closure of both the anterior (right coronary) and posterior (non coronary) cusps *AV* = aortic valve *ECG* = electrocardio gram *C* = carotid pulse tracing *PCG* = phonocardiogram

cant progression in the patient s symptoms cardiac surgery was advised

At surgery a deformed tricuspid aortic valve was present The cusp commissures were fused at their origins and the valve cusps were thickened with the free edges of the cusps folded back upon themselves to create a predominantly insufficient minimally stenotic aortic valve Mild cusp calcifi cation was apparent on gross examination No evidence of recent or healed endocarditis was present A discrete fibrous diaphragm was located approximately *5 mm below the aortic* valve annulus This diaphragm appeared stenotic admitting only the tip of an index finger The aortic valve cusps and the diaphragm were excised and a cloth covered Starr Edwards prosthesis was implanted

The microscopic pathology of the aortic valve cusps revealed areas of fibrosis and calcification The subaortic diaphragm was composed of dense connective tissue with no muscular elements

Discussion

We present this case as an unusual example in the middle aged adult of a congenital subaortic *diaphragm causing fixed LVOT obstruction and a*

probably acquired deformity of the aortic valve associated with moderate aortic insufficiency We illustrate the difficulty in determining the precise location and nature of LVOT lesions preoperatively by clinical hemodynamic and angiographic methods We emphasize the value of M mode cardiac ultrasonography as a noninvasive method to evaluate the aortic valve and LVOT

The M mode echocardiographic features of fixed subaortic LVOT obstruction have been delineated In these cases an early systolic rapid cusp movement toward closure frequently with maintenance of this semi closed position for the duration of systole is present (Fig 2A) Aortic valve structure is normal by echocardiography In this patient the aortic valve was structurally abnormal with multiple diastolic cusp echoes indicative of thickening and calcification The preservation of systolic cusp opening however suggested the absence of a significant valvular systolic pressure gradient The remarkable feature is that enough systolic cusp mobility remained to demonstrate an early and rapid systolic movement toward closure of the right coronary cusp This early systolic preclosure of the right coronary cusp in the absence of clinical or echocardiographic features of hypertrophic obstructive cardiomyopathy (HOCM) mitral regurgitation or ventricular septal defect with left to right shunting suggested fixed subaortic LVOT obstruction The flutter of the anterior leaflet of the mitral valve confirmed aortic insufficiency a condition frequently associated with congenital discrete subaortic stenosis

Various patterns of aortic valve pre closure have been described with cardiac conditions other than congenital fixed subaortic obstruction [7] HOCM with dynamic LVOT obstruction may demonstrate rapid full amplitude systolic opening of the aortic valve cusps followed by gradual movement of one or both cusps toward closure in early or mid systole The cusps maintain this semi closed position for a variable time in mid systole and may demonstrate coarse systolic flutter There is gradual reopening of the cusps in late systole (Fig 2B) In some cases of mitral regurgitation with reduced cardiac output or ventricular septal defect with left to right shunting the aortic valve cusps may show a full amplitude systolic cusp separation followed by a gradual drifting movement of the cusps toward closure and fine systolic flutter for the remainder of systole (Fig 2C) Gradual movement toward closure in early or mid systole with gradual reopening for the remainder of systole of the right coronary cusp has been described with right coronary sinus of Valsalva fistulae [7]

In this patient the process causing cusp thickening with mild calcification commissural fusion and folding back of the cusp free edges is not known We speculate that the aortic valve deformity was acquired either through the long term effects of the subvalvular diaphragm with trauma to the aortic valve cusps from the high velocity jet striking the cusps or perhaps chronic rheumatic valvulitis Aortic valve cusp thickening with rolling back of the edges but without commissural fusion has been described at the time of surgery or autopsy in older patients with discrete subaortic stenosis complicated by aortic valvular endocarditis [3] However in previous echocardiographic descriptions of fixed subaortic stenosis aortic valve structure has been normal

The localization of a subaortic diaphragm by cardiac catheterization depends on the precise localization of a fixed subvalvular systolic pressure gradient by catheter withdrawal across the LVOT [9] If the subaortic diaphragm is immediately subjacent to the aortic valve it may be difficult to distinguish a valvular from a subvalvular systolic pressure gradient In this patient the transseptal technique was performed without the benefit of withdrawal pressures across the LVOT In addition selective left ventricular angiography by the transseptal method with reflux of contrast dye into the left atrium did not allow optimal visualization of the LVOT to detect a subaortic diaphragm [1]

In summary we present a middle aged white male with a congenital subaortic diaphragm and a probably acquired aortic valve deformity documented at surgery The lesions were associated with moderate LVOT obstruction and aortic insufficiency The abnormal structure of the aortic valve cusps with multiple diastolic echoes and the abnormal early systolic pre closure movement of the right coronary cusp on M mode echocardiography suggested both lesions preoperatively We emphasize the value of noninvasive M mode cardiac ultrasonography in the evaluation of the LVOT and aortic valve as an aid in the differential diagnosis of lesions associated with LVOT obstruction and aortic insufficiency

Summary

The M mode echocardiographic features of aortic valve structure and motion in a 45 year old male with combined congenital subaortic diaphragm and acquired deformity of the aortic valve are described Clinical, hemodynamic, and angiographic studies suggested calcific aortic valve disease with stenosis and insufficiency, but the additional presence of a subaortic diaphragm was not appreciated Cardiac ultrasonography demonstrated multiple central diastolic aortic valve cusp echoes consistent with a thickened, calcified tricuspid aortic valve Despite calcification of the cusps however, enough systolic cusp excursion remained to demonstrate an early systolic rapid movement toward closure of the right coronary cusp—a finding suggestive of fixed subvalvular obstruction Surgery confirmed a discrete subaortic diaphragm and a tricuspid thickened mildly calcified aortic valve with fusion of the cusp commissures at their origins and rolling back of the cusp edges The value of echocardiography in the evaluation of the left ventricular outflow tract and aortic valve is emphasized

The authors thank Dr Arthur Moss for allowing us to study his patient and Mrs Summer King for her secretarial assistance

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Granulomatous myocarditis secondary to cornstarch

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Cornstarch was introduced as a lubricating powder for surgical gloves over twenty years ago. The initial animal experiments indicated that starch was satisfactorily absorbed in the abdominal cavity of animals.[1,2] Nevertheless, reports of postoperative granulomatous inflammation due to starch glove powder soon appeared in the literature.[3-6] To date over 60 such cases have been reported in the American, English, and European literature. Starch peritonitis has been associated with abdominal pain, bowel obstruction due to abdominal adhesions, and fever. Symptoms have occurred as early as 15 days postoperatively.

This paper deals with a granulomatous myocarditis due to starch powder following cardiac catheterization and replacement of the mitral valve.

Case report

P. K., a 44-year-old white female, presented with a history of her first attack of rheumatic fever at age 9 and repeated episodes until the age of 28. The patient was free of cardiac symptoms until March, 1973, when she developed pedal edema, generalized fatigue, and moderate dyspnea on exertion. She was treated with digoxin and diuretics and improved. She was rehospitalized a month later with ascites, ankle edema, orthopnea, and paroxysmal nocturnal dyspnea.

Physical examination revealed a 2+ parasternal lift, a palpable and accentuated S_1, and a holosystolic Grade IV/VI murmur with a Grade II/VI mid-diastolic rumble at the apex. S_2 was physiologically split and P_2 was accentuated. A loud S_3 was present at the apex. Other laboratory data were unremarkable. Chest x-ray revealed cardiomegaly and left atrial enlargement, a prominent pulmonary artery, and calcification of the mitral annulus. ECG showed sinus rhythm, right bundle branch block, right axis deviation, and first degree A-V block. The patient underwent cardiac catheterization on April 27, 1973, which revealed severe mitral regurgitation with severe pulmonary hypertension. On May 2, 1973, the patient underwent an uneventful valve replacement with a Bjork-Shiley valve. A rhythm strip on May 4, 1973, revealed nonparoxysmal junctional tachycardia; later on the same day complete A-V dissociation was observed. On May 5, 1973, rhythm strip was consistent with atrial fibrillation with a rapid ventricular response. This responded to digoxin intravenously with controlled response. The rest of the postoperative course was uneventful. On the ninth postoperative day, the patient experienced a sudden onset of chest pain with hypotension, diaphoresis, and distended neck veins which were thought to be due to pulmonary emboli. The ECG at the time revealed atrial fibrillation with rapid ventricular response. Treatment was not effective and the patient died shortly thereafter.

Pathologic findings. The autopsy was restricted to examination of the thoracic organs. The pericardial sac was open from previous surgery and the epicardium reddened and partly covered by fibrin deposits. The heart weighed 780 Gm. and showed marked hypertrophy of both ventricles and moderate hypertrophy and dilation of the left atrium. A healing incision was noted across the medial and posterior wall of the left atrium. There were multiple flat red-tan mural thrombi in the left atrium, the largest of which was elongated, measuring 10 by 3 cm. (Fig. 1). This thrombus was attached at one end near the incision with the other end loose and apparently occluding completely the mitral orifice (Fig. 2). The Bjork-Shiley valve appeared to have been functioning normally.

Microscopic examination of numerous sections revealed a widespread focal inflammatory reaction involving all chambers of the heart. The main features were interstitial cellular

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Fig 1 Multiple mural thrombi of left atrium the largest of which covers the mitral orifice



Fig 2 The flapping mural thrombus has been lifted off the mitral orifice

infiltrates consisting predominantly of lymphocytes with some monocytes and occasional eosinophils neutrophils and plasma cells and small granulomas with multinucleated giant cells and focal myofiber damage or replacement (Fig 3) In addition to the myocardium granulomas were found in the endocardium and rarely in the epicardium There was also an organizing fibrinous pericarditis The giant cells were of the foreign body type A rare giant cell resembled myogenic giant cell In the granulomas both inside and outside giant cells an occasional rounded foreign body was noted measuring up to about 14 µm in diameter (Fig 4) as well as some smaller irregularly shaped particles of similar foreign material These foreign bodies were light bluish in the hematoxylin and eosin stained sections and were inconspicuous These particles stained red with the periodic acid Schiff reagent (PAS) dark bluish-black with Gram s iodine and exhibited Maltese cross birefringence under polarized light (Fig 5) They were always associated with inflammatory reaction In addition to these granules some anisotrophic fiber like material was noted inside a rare small artery (Fig 6) These fibers were also associated with giant cell reaction but they did not stain with PAS In some of the sections granular birefringent material appeared to have broken through the vessel wall (Fig 7) No starch granules were found intravascularly Stains for fungi were negative The granules found in the heart were identical with starch granules from glove powder (Fig 8)

Examination of numerous sections from a dozen hearts from patients who had undergone cardiac catheterization



Fig 3 Interstitial and granulomatous inflammation of left ventricular wall (Original magnification about ×?00)

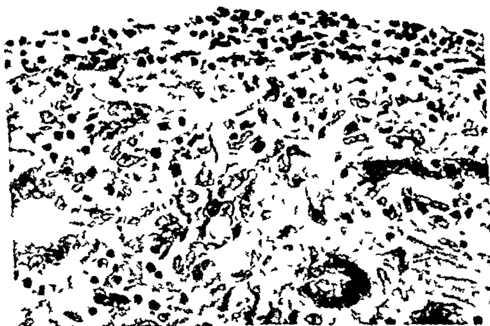


Fig 4 Endo and myocardium left ventricle Granulomatous inflammation The arrow points to a foreign body (Original magnification about ×500)

and/or cardiac surgery revealed an occasional intra or extra arterial granuloma around anisotropic fibers but no starch granules were identified

Sections from the left atrium showed recent mural thrombi There was some edema of the underlying endocardium with infiltration of an occasional neutrophil Also noted in some of the sections was a subendocardial layer of granulation tissue parallel to the endocardial surface No granulomas were noted in the endocardium of the left atrium The myocardium in addition showed moderate hypertrophy and scattered small scars, mainly perivascular with a rare apparent inactive fibrotic Aschoff body The aortic cusps revealed hyaline fibrosis with some vascularization There was mild to moderate coronary atherosclerosis Sections of lung showed chronic passive congestion but no granulomas.

Discussion

Although the inflammatory reaction of the heart in this case was widespread the number of starch granules was relatively small In some of the granulomatous nodules no starch granules were found and in others as a rule there was only one granule present Some of the granules appeared to be fragmented or partly absorbed In animal experiments starch granules have been reported completely absorbed within three weeks[1] The rate of absorption in humans is not known

Surgical patients are probably often exposed to

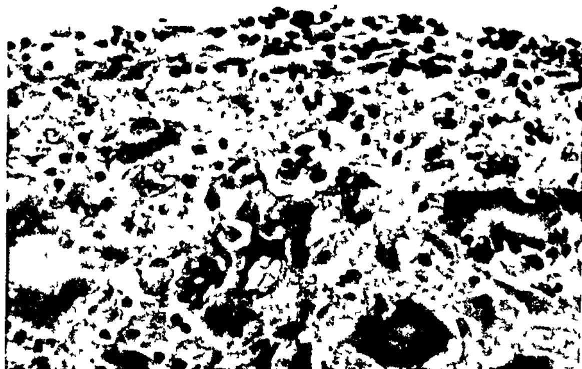


Fig 5 Same field as in *Fig 4* viewed under polarized light The foreign body is birefringent and shows a Maltese cross



Fig 6 Anisotrophic fiber like material inside a small artery Inflammatory reaction with some multinucleated giant cells in the endothelium (Original magnification about ×200)

starch glove powder Even if the gloves are care fully washed before the surgical procedure gloves commonly break during surgery releasing the lubricating glove powder The amount of contamination is undoubtedly an important factor but the reaction to the same dose is likely to be very variable in different patients Perhaps the rate of absorption varies from one patient to another Skin test for hypersensitivity to starch in patients with starch peritonitis have varied from negative to equivocal [10, 11] However Lietze Rowe and Rowe[1] have demonstrated a high incidence of passive hemagglutination antibodies to potato and tapioca starch in normal persons The histo logic picture in our case was that of a typical foreign body granuloma but eosinophils were inconspicuous

Although the symptoms of some of the patients with starch granulomatous peritonitis have been quite severe and prolonged almost all of the reported cases have recovered The death of our patient was due to a sudden mitral occlusion secondary to a flapping ribbon shaped mural thrombus in the left atrium Whether the granu lomatous inflammation contributed to the forma tion of the mural thrombi and what role a direct trauma to the endocardium from the surgical procedure played cannot be settled The suben



Fig 7 Birefringent material apparently breaking through a vessel wall (Original magnification about ×200)

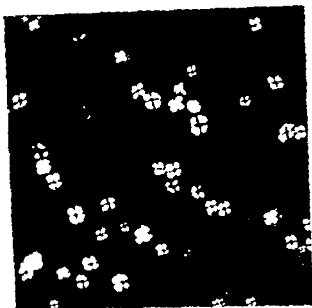


Fig 8 Glove powder under polarized light (Original magnification about ×?00)

docardial layer of granulation tissue on the left atrium was probably a secondary reaction to edema of the loose subendocardial tissue This type of a reaction was described many years ago in connection with a giant cell myocarditis [3]

There are two possible sources of the starch granules in this case The starch granules might have been introduced into the coronary circulation during the cardiac catheterization or at the time of the valve replacement During catheterization contamination could have occurred from the irrigation solution or contrast media which may have been contaminated with starch powder Introduction of starch granules into the circulation has been known to occur through contamination of syringes and catheters and anisotropic intra arterial fibers resembling cotton or cellulose fibers have been demonstrated quite frequently in various organs at autopsy in patients who have had cardiac surgery or catheterization [5]

The myocarditis in this case was classified as granulomatous myocarditis rather than giant cell myocarditis since a known foreign body was established as the causative agent Myogenic giant cells may otherwise be difficult to differentiate from foreign body giant cells and the relationship between giant cell myocarditis and granulomatous myocarditis of unknown etiology is very unclear indeed

Summary

A 44 year old white female with chronic rheumatic heart disease and mitral insufficiency was admitted to the hospital for cardiac catheterization and mitral valve replacement On the ninth postoperative day the patient experienced a sudden onset of chest pain hypotension and died shortly thereafter Autopsy revealed multiple mural thrombi of the left atrium one of which occluded the mitral orifice Histologic examination showed a granulomatous and non specific interstitial myocarditis involving all chambers of the heart In the granulomas both inside and outside giant cells, rounded foreign bodies were noted which stained light blue with hematoxylin and eosin red with the periodic acid Schiff reagent dark bluish-black with Gram s iodine and showed Maltese cross birefringence under polarized light These particles were identical with starch granules from surgical glove powder The cause of death was acute mitral occlusion from a flapping mural thrombus

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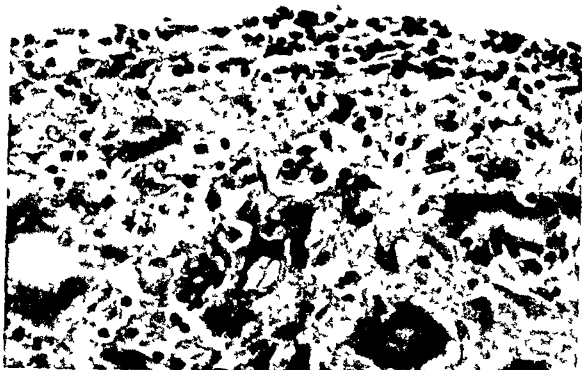


Fig 5 Same field as in *Fig 4* viewed under polarized light The foreign body is birefringent and shows a Maltese cross



Fig 6 Anisotrophic fiber like material inside a small artery Inflammatory reaction with some multinucleated giant cells in the endothelium (Original magnification about ×200)

starch glove powder Even if the gloves are carefully washed before the surgical procedure gloves commonly break during surgery releasing the lubricating glove powder The amount of contamination is undoubtedly an important factor but the reaction to the same dose is likely to be very variable in different patients Perhaps the rate of absorption varies from one patient to another Skin test for hypersensitivity to starch in patients with starch peritonitis have varied from negative to equivocal [10, 11] However Lietze Rowe and Rowe[1] have demonstrated a high incidence of *passive hemagglutination* antibodies to potato and tapioca starch in normal persons The histologic picture in our case was that of a typical foreign body granuloma but eosinophils were inconspicuous

Although the symptoms of some of the patients with starch granulomatous peritonitis have been quite severe and prolonged almost all of the reported cases have recovered The death of our patient was due to a sudden mitral occlusion secondary to a flapping ribbon shaped mural thrombus in the left atrium Whether the granulomatous inflammation contributed to the formation of the mural thrombi and what role a direct trauma to the endocardium from the surgical *procedure played cannot be settled The suben*

Platelet functions in patients with aortic ball valves

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Patients with aortic ball valves have a high incidence of arterial thromboembolic complications, and the emboli are usually derived from thrombi located on the prosthetic valve itself. Anticoagulant treatment cannot fully prevent these complications, although intense therapy has been found to offer some protection. The tendency to arterial thrombus formation in such patients focused our attention on the function of their blood platelets.

Another characteristic finding in patients with aortic ball valves is intravascular hemolysis, which is almost invariably increased to a greater or lesser degree. The possibility that hemolysis may modify the function of blood platelets and thereby the hemostatic and thrombotic mechanisms is indicated by Hellem's discovery that red cells contain a factor necessary for platelet retention in glass bead columns, later identified to be adenosine diphosphate (ADP).

The purpose of this investigation was to study platelet functions in a larger series of patients with aortic ball valve prostheses and to relate the findings to the degree of intravascular hemolysis as well as to the occurrence of arterial thromboembolic complications. Results from a preliminary study have been published previously.

Materials and methods

Patients with single Starr-Edwards aortic ball valves were studied. Such valves were implanted in 253 patients at our center from 1967 until 1970, and 169 of the 175 patients still alive reported for an extensive follow-up examination in 1972. Two series of Starr-Edwards aortic valves were used: type 1200 with silicone rubber ball and metal cage. Most of the platelet function studies were done before or at the follow-up examination. After this the patients entered a controlled clinical trial and were given either acetylsalicylic acid or placebo in addition to their anticoagulant therapy. Platelet function tests could therefore not be performed later, since the results could disclose the type of drug given.

The platelet counts were determined in all subjects, whereas the other tests were done in a varying number of unselected patients. Platelet function was also evaluated in healthy individuals, mainly hospital personnel selected to obtain the best possible similarity to the patients with regard to sex and age distribution. The number of patients and healthy persons subjected to the different tests is specified in the Results section. In addition, the bleeding time was measured in 23 patients receiving anticoagulants for other reasons than valve implantation, including postoperative prophylaxis after orthopedic surgery, coronary heart disease, peripheral arterial disease, and atrial fibrillation. Platelet survival was studied in seven patients with aortic valve disease unoperated upon.

The degree of intravascular hemolysis was estimated from the serum lactate dehydrogenase (LDH) activity at 25° C as earlier described. The following platelet function tests were done. The bleeding time was measured from two incisions by Borchgrevink and Waaler's modification of Ivy's method by one of us (J. D.). The cuts were approximately 1 cm long, but the depth was adjusted so that instead of a 1 mm depth a blood drop the size of a matchhead emerged in 30 seconds. Platelets were counted in a hemocytometer by a modification of Nygaard's method. Platelet adhesiveness was determined in native blood by the modified method of Hellem.

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The mean bleeding time in healthy individuals was 4.8 minutes and the standard deviation (S.D.) 1.2 giving a normal range (mean ± 2 S.D.) of 2.4 to 7.2 minutes. The precision of the method could be estimated since duplicate incisions were made and the coefficient of variation was calculated to be 17.5 in normal subjects and 15.3 in valve patients.

The bleeding time was prolonged on average by 2.4 minutes in patients with valves of type 2300 which is statistically highly significant whereas a moderate nonsignificant prolongation was found in those with valve 1200 (Table II). In the heterogeneous group of patients on anticoagulants a slight but significant increase was found. Compared with this group the increase of the mean bleeding time in individuals with valve type 2300 was, however, also highly significant ($p < 0.001$). The tests were repeated in nine patients with bleeding times in the upper range on average 8.8 minutes after 2 to 12 months in order to study the consistency of the prolongation. The values were well reproducible since the coefficient of variation of the difference was as low as 10.1.

The mean platelet count was moderately but significantly lower in both groups as compared with that of normal subjects (Table III), the range in healthy individuals being 140,000 to 309,000.

The mean platelet adhesiveness in normal subjects was 71.8 per cent and the S.D. 8.6, the normal range therefore being 55 to 89 per cent. Platelet adhesiveness was markedly reduced in valve patients and most pronounced in those with valves of type 2300 (Table IV). The difference between the mean values in the two patient groups was also highly significant ($p < 0.001$). The variability of the adhesiveness values was estimated by repeated testing after 1 week to 2 years in 17 patients. The mean adhesiveness in these was 28 per cent and the coefficient of variation of the differences was 28.2.

The approximate mean numbers of adhesive and nonadhesive platelets could be calculated since the mean total platelet counts and the mean platelet adhesiveness were known in normal subjects and valve patients. Not only were the numbers of adhesive platelets reduced in the patients but nonadhesive platelets were considerably increased.

An inverse linear relationship was found between adhesiveness and bleeding time in 17 valve patients (Fig. 1), the correlation coefficient of the regression line being −0.57 ($0.05 > p > 0.01$). The bleeding time and actual number of adhesive platelets correlated equally well. A comparison between serum LDH levels and platelet adhesiveness was made in 46 patients with ball valves and a significant inverse correlation ($p > 0.01$) was found (Fig. 2).

The studies on platelet aggregation did not reveal marked deviations from the normal response. The slightly reduced rate of primary aggregation initiated with ADP in patients with valve type 2300 did not reach statistical signifi

Table V The maximal rate of reversible platelet aggregation induced by 0.7 μM of ADP and of irreversible aggregation initiated with 2.1 μg per milligram of collagen in per cent of the normal response

	No. of subjects	*Aggregation (% of normal)*		Compared with normal
		Mean	*S.E.M.*	
ADP-induced aggregation				
Healthy individuals	57	100.1	2.7	
Patients, valve 1200	13	96.5	6.7	N.S.
Patients, valve 2300	32	90.2	4.4	N.S.
Collagen induced aggregation				
Healthy individuals	51	99.9	2.9	
Patients valve 1200	12	98.9	6.2	N.S.
Patients valve 2300	32	[illegible]	3.6	p = 0.005

Table VI Platelet half life in patients with unoperated aortic valvular disease and Starr Edwards aortic ball valves.*

	No. of subjects	*Platelet half life (days)*	
		Mean	*S.E.M.*
Healthy individuals	[illegible]	3.78	0.0[illegible]
Unoperated valve disease	7	3.78	0.24
Starr Edwards aortic valves	17	3.4[illegible]	0.13

*For comparison, the half life in normal men between 40 and 70 years of age is calculated from Abrahamsen study.

Table I Serum LDH levels in healthy individuals and patients with Starr Edwards aortic ball valve prostheses*

	No of subjects	*Serum LDH (U/L)* Mean	SEM	Compared with normal
Healthy persons	60	120 5	2 7	
Patients valve 1200	21	269 9	28 3	$p < 0001$
Patients valve 2300	48	580 7	51 7	$p < 0001$

Level of significance of differences between mean values in normal subjects and in valve patients

Table II Bleeding time in healthy individuals patients with Starr Edwards aortic ball valves and other patients on anticoagulants*

	No of subjects	*Bleeding time (min)* Mean	SEM	Compared with normal
Healthy individuals	25	4 8	0 24	
Patients valve 1200	10	5 5	0 51	N S
Patients valve 2300	22	7 2	0 38	$p < 0001$
Others on anti coagulants	17	5 6	0 23	$p < 001$

The number of subjects mean value in minutes and standard error of the mean are listed and the level of significance of the differences between the mean values in normal subjects and patients is calculated (N S = not significant)

Platelet aggregation was estimated in platelet rich plasma (PRP) by the turbidimetric method described by Born[17] with the Unigalvo EEL titrator (Evans Electroselenium Ltd Essex England) *PRP* was obtained by centrifugation of citrated blood at 300 × g for 15 minutes Aggregation was initiated with collagen ADP and epinephrine in final concentrations of 2 1 μg per milliliter, 0 7 μM and 3 64 μM respectively The curves were always recorded in this sequence, adding collagen suspension to PRP 20 minutes after blood withdrawal The maximal rate of collagen and ADP induced aggregation was estimated This response has been found to be proportional to the platelet count in normal subjects (Dale and Lund Ruse To be published) The rate in each patient was therefore calculated

Table III Platelet counts in healthy individual and patients with Starr Edwards aortic bal valves *

	No of subjects	*Platelets (per μl)* Mean	S.E.M	Compared with normal
Healthy individuals	28	224 200	8 000	
Patients valve 1200	46	183 000	7 200	$p < 0001$
Patients valve 2300	111	189 100	5 600	$p < 0001$

Number of subjects, mean values and standard error of the mean. Level of significance of the difference between normal subjects and patients.

Table IV Platelet adhesiveness in healthy individuals and patients with Starr Edwards aortic ball valves

	No of subjects	*Adhesiveness (%)* Mean	SEM	Compared with normal
Healthy individuals	22	71 8	1 8	
Patients valve 1200	21	50 9	3 7	$p < 0001$
Patients valve 2300	48	27 2	2 3	$p < 0001$

in per cent of the normal value at the actual platelet count Whether epinephrine induced irreversible secondary aggregation was evaluated from the shape of the curves

Platelet survival was determined according to Abrahamsen s[18] method by labeling autologous platelets with $^{51}CrO_4$ and reinjecting them The platelet half life was determined from 16 hours after the injections and until the radioactivity had reached half of the 16 hour value

Results

Intravascular hemolysis as reflected by the serum LDH values was increased in nearly all patients with prosthetic valves and significantly higher enzyme levels ($p < 0001$) were found in patients with valve type 2300 than in those with valves of series 1200 (Table I) which is in accord with our earlier results[8] Only LDH values from patients in whom platelet adhesiveness was also determined are presented here

Table VII Comparison of platelet functions in ball valve patients with and without arterial thromboembolic complications with level of significance of the differences

	Patients with thromboembolism			*Patients without thromboembolism*			
	No	*Mean*	*SEM*	*No*	*Mean*	*SEM*	*Significance*
Platelets (per μl)	39	179,200	8 100	113	193 000	5 800	N S
Bleeding time (min)	6	6 4	0 46	25	6 8	0 41	N S
Adhesiveness (%)	17	29 4	4 3	40	37.3	3.3	N S
ADP induced aggregation (% of normal)	11	89 8	5 3	34	92.7	4 5	N S
Collagen induced aggregation (% of normal)	11	89 8	7 4	32	87.3	3.2	N S
Platelet half life (days)	4	3 63	0 22	13	3 56	0 17	N S

Table VIII Comparison of platelet functions in ball valve patients with and without bleeding episodes with level of significance of the differences

	Patients with bleeding			*Patients without bleeding*			
	No	*Mean*	*SEM*	*No*	*Mean*	*SEM*	*Significance*
Platelets (per μl)	19	1 6400	13 900	133	191,300	5 000	N S
Adhesiveness (%)	6	25 3	4 0	67	35 4	2.5	$p < 0.05$
Bleeding time (min)	8	6 7	0 55	24	6 7	0 4	

of hemolysis as expressed by serum LDH was poor ($r = 0.28$, $p > 0.10$)

The incidence of arterial thromboembolic complications in the patients before and after this study has been recorded Platelet functions were compared in patients who suffered such complications and those who did not (Table VII) None of the differences observed was statistically significant The number of observations was however so small in the group with thromboembolism with regard to some of the tests that a statistical evaluation was of limited value since the investigation was performed in unselected patients

Some patients developed bleeding episodes during the subsequent controlled clinical trial mostly gastrointestinal bleeding in those receiving acetylsalicylic acid in addition to anticoagulants[2] Platelet counts adhesiveness and bleeding time were compared in patients with and without bleeding episodes (Table VIII) and significantly lower mean platelet adhesiveness was found in those who later suffered from bleeding

Discussion

The study has demonstrated abnormal platelet function in patients with aortic ball valve prostheses with most marked disturbances of platelet adhesiveness and bleeding time whereas platelet counts irreversible platelet aggregation and platelet survival deviated slightly from normal

The mean value and distribution of platelet counts in healthy individuals are in good agreement with the findings of others[2] The slightly reduced mean platelet number in the ball valve patients may be related to the moderately shortened platelet survival Decreased amounts of circulating platelets after localized thrombosis have been found by some[22] but not by others[23]

The mean normal bleeding time was approximately 2 minutes shorter than that originally reported [5] but the method was slightly modified Moreover our normal values correspond well with those of others using comparable techniques [1,2] and the precision as well as the reproducibility were acceptable [1,27] The prolongation of the bleeding time in patients with valves of type 2300 indicates a defect in the hemostatic mechanism that may render them prone to bleeding Acetylsalicylic acid causes a marked additional prolongation[2] and might therefore induce a particularly strong bleeding tendency in such patients

Platelet adhesiveness was markedly reduced in our patients whereas others have found normal

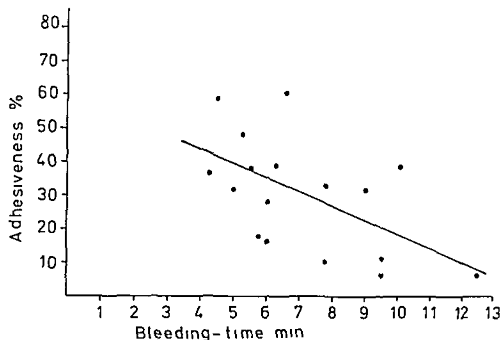


Fig 1 Relation between platelet adhesiveness and bleeding time in 17 patients with Starr Edwards aortic ball valve prostheses The formula for the regression line is Adhesiveness = −4 28 × bleeding time +60 1 Coefficient of correlation r = −0 57

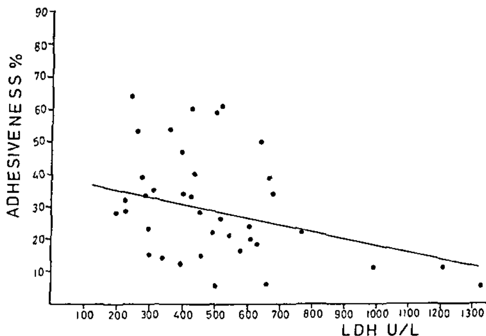


Fig 2 Relation between platelet adhesiveness and serum LDH levels

cance However the mean maximal rate of irreversible aggregation induced by collagen was moderately—but significantly—lower in these patients (Table V) Epinephrine elicited secondary, irreversible aggregation in 64 per cent of the patients with prosthetic valves as compared to 89 per cent of the healthy individuals a statistically significant difference (0 02 > p > 0 01)

The platelet half life was insignificantly shorter in patients with ball valves than in those with unoperated upon aortic valve disease (Table VI)

Lacking a normal material of our own we compared our values with those of individuals between 40 and 70 years of age from Abrahamsen s[1] study The mean value in these was exactly the same as in our own unoperated upon patients whereas a significant difference (p = 0 02) was found when a comparison was made with our valve patients Since only three patients had valves of type 1200 a separate evaluation of the survival in these could not be made The inverse correlation between platelet survival and degree

damage could reduce platelet adhesiveness possibly the most delicate and vulnerable reactivity measured in a large proportion of the platelets A stronger trauma could cause reduced irreversible aggregation or removal of platelets from the circulation giving slightly reduced platelet numbers and shortened survival According to this intravascular hemolysis and disturbed platelet function are parallel phenomena induced by mechanical trauma of red cells and platelets respectively

Platelet functions were the same in patients who developed arterial thromboembolism and those who did not but our material was too small with regard to platelet survival to allow conclusions In a larger series of patients with Starr Edwards aortic ball valves a slightly—but significantly—shorter survival was found in those who had thromboembolic episodes [3]

Our findings indicate that the occurrence of arterial thrombosis is not chiefly determined by individual differences in platelet reactivity the important factors triggering thrombus formation probably being the foreign material represented by the valve itself [5] and the turbulence of the blood stream caused by the valve However although the patients with valves of type 2300 have a higher degree of hemolysis and lower platelet adhesiveness than those with valve type 1200 they have a much lower incidence of arterial thromboembolic complications [1] Although the difference in thrombogenicity has been attributed to the cloth covering of the cage in the newer valves the low number of adhesive platelets could offer some protection against thrombus formation Thus the reduced platelet reactivity in patients with aortic ball valves may be regarded as a defense against arterial thrombus formation

Summary

Platelet functions were studied in normal subjects and patients with single Starr Edwards aortic ball valves of series 1200 and 2300 The most pronounced changes were found in platelet adhesiveness measured with Hellem s modified method The mean percentage of adhesive platelets was reduced from 71 8 in normal subjects to 50 9 in patients with valve type 1200 and to 27 2 in those with type 2300 An inverse correlation was found between platelet adhesiveness and the degree of intravascular hemolysis as reflected by serum LDH levels The mean bleeding time was significantly prolonged in patients with valve 2300 and the individual values correlated inversely to the adhesiveness The mean values of platelet counts, of irreversible aggregation induced by collagen or epinephrine and of platelet survival were all moderately—but significantly—reduced as compared to normal The most important mechanism behind the disturbed platelet reactivity is probably mechanical damage of the platelets by the valve whereas refractoriness of platelets toward ADP liberated from red cells as well as consumption of adhesive platelets by thrombus formation is thought to have limited influence on platelet behavior Platelet function was altered to the same extent in patients with a history of arterial thromboembolic complications as in those without The disturbed platelet reactivity may predispose to bleeding but may also offer some protection against arterial thromboembolism

We are indebted to Dr K Rootwelt Section of Nuclear Medicine for the survival studies, and to Mrs A L Almaas and Mrs Aa Lund Rise for skilled technical assistance

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values with a modified Salzman's method after mitral valve implantation. The inverse relationship between number of adhesive platelets and bleeding time is in accord with the original discovery of Hellem and associates[7] and supports the theory that adhesive platelets are important for primary hemostasis. This is further indicated by the relation between in vivo and in vitro adhesiveness and by some similarities between the structure of the primary platelet plug[30] and the platelet aggregates retained by glass bead columns.[31] Thus, the prolongation of the bleeding time observed is most probably due to the reduced number of adhesive platelets.

The primary aggregation induced by ADP probably partly reflects a similar platelet reaction as does the adhesiveness test since platelet retention is also dependent upon available ADP[1] and since the structure of retained aggregates closely resembles that of platelets aggregated by ADP.[31] However, the primary ADP induced aggregation was normal in our patients whereas the retention was reduced. A likely explanation is that the adhesiveness test to a considerable extent reflects the in vivo reactivity of the platelets, whereas the primary aggregation does not. For adhesiveness measurements, native blood is used directly after careful withdrawal[1] and rough handling of the blood reduces retention considerably, probably through liberation of ADP.[32] Before testing aggregation, however, the blood is exposed to addition of citrate, to centrifugation, and finally to rather violent mechanical stirring. These procedures in addition to the time from blood withdrawal until aggregation is recorded most probably influence the platelets to such an extent that the original reactivity is seriously altered. The secondary irreversible platelet aggregation is possibly less influenced by the procedure than the more sensitive primary aggregation. Irreversible aggregation has been reported to be normal in patients with mitral valve prostheses.[9] The substance 2,3-diphosphoglycerate, which is present in red cells and liberated during intravascular hemolysis, inhibits the platelet release reaction and irreversible aggregation[33] and might influence aggregation in patients with prosthetic valves.

Platelet survival has been found to be normal in patients with unoperated-upon valvular disease.[14] Since our mean platelet half life in such platelets was equal to the mean normal value in Abrahamsen's[19] study for the same age group, a comparison between the latter material and ours seemed justified. The moderate shortening of platelet survival in our valve patients is in good agreement with the results from other studies,[34,35] whereas the more pronounced reduction reported by one group may be due to methodological differences. The exponential slopes of the survival curves from several patients indicate random disappearance of the platelets.

Three mechanisms for disturbed platelet function in patients with prosthetic valves have been suggested:[1] Refractoriness toward ADP liberated from red cells, consumption of adhesive platelets during thrombus formation, and mechanical trauma of platelets by passage through the valve. After exposure of platelets to ADP, further addition of ADP combined with mechanical stirring results in a lowered aggregating response, the platelets having become refractory.[3,19] Platelet retention in glass bead columns is dependent upon ADP from disrupted red cells,[10] from platelets adhering to the beads and undergoing release,[40] or from both sources. Retention is inhibited by addition of ADP prior to the testing,[31] by rapid transfer of blood between syringes or slow centrifugation,[3] or by intravenous infusion of water causing intravascular hemolysis.[41] The destruction of red cells by the valves could possibly provide ADP in concentrations sufficiently high near the valves to induce platelet refractoriness. However, the rate of continuous hemolysis is low as compared to that reported after water infusions.[4,41] ADP is immediately diluted by the blood stream and it is rapidly cleared from plasma.[42,43] It therefore seems unlikely that ADP liberation from red cells can explain the disturbances in platelet function.

Consumption of adhesive platelets by thrombus formation could possibly induce a certain reduction in the number of these platelets but not to the extent found in patients with valves of type 2300. Moreover, the incidence of arterial thromboembolic complications was lower in these patients than in those with valve type 1200.[1] Finally, such consumption would not induce the actual increase of nonadhesive platelets seen in the patients.

The most important mechanism is therefore probably mechanical damage of the platelets by the prosthetic valves, which could produce all the changes observed in platelet behavior. A slight

damage could reduce platelet adhesiveness possibly the most delicate and vulnerable reactivity measured in a large proportion of the platelets A stronger trauma could cause reduced irreversible aggregation or removal of platelets from the circulation giving slightly reduced platelet numbers and shortened survival According to this intravascular hemolysis and disturbed platelet function are parallel phenomena induced by mechanical trauma of red cells and platelets respectively

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Clinical manifestations of mitral annulus calcification, with emphasis on its echocardiographic features

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Several descriptions of the pathologic anatomy of mitral annulus calcification (MAC) have appeared over the past seven decades. The various authors observed a striking distortion of the anatomy of the left ventricle and the mitral valve apparatus by MAC, especially when the latter was massive. They also noted a high incidence of MAC in the elderly and its frequent association with cardiac murmurs, cardiac conduction defects, and cardiac failure. Nevertheless, most textbooks of cardiology and internal medicine have either ignored MAC completely or have given it only passing mention as one of the various causes of intracardiac calcification seen on the chest roentgenogram.

The detection of MAC by reflected ultrasound has been reported recently, and in fact echocardiography may be more sensitive than radiography in the diagnosis of MAC. The recognition of MAC on echocardiograms is not merely of academic interest but is also of practical clinical importance because the patterns resulting from MAC can be mistaken sometimes for those of certain common cardiac conditions such as mitral stenosis, idiopathic hypertrophic subaortic stenosis (IHSS), and pericardial effusion.

We have reviewed the salient clinical and echocardiographic features of MAC based on our observations in a series of 38 patients studied in our echocardiography laboratory during the last two years. We report here abnormalities we have detected and discuss their relationship to the distorted left ventricular (LV) anatomy and altered mitral valve motion that occur in patients with MAC.

Incidence

MAC is found in about 8.5 per cent to 10 per cent of adult autopsies, almost always in patients over 50 years of age. It occurs 1.6 to 3.8 times more frequently in women than in men. Its relationship to the aging process is emphasized by the fact that it is found at the time of autopsy in 17 per cent of men and 43 per cent of women over 90 years.

Roberts and Perloff, however, found an equal sex incidence in their necropsy series of 87 cases of MAC. Of these, 25 were under 65 years of age, and eight were under 40. It is noteworthy that all eight young patients in this series had associated systemic diseases (Marfan's syndrome in three, Hurler's syndrome in two, and metabolic disturbances with hypercalcemia in three). In women MAC tends to be more extensive and severe than in men.

Pathology

Several descriptions of the pathologic anatomy of MAC were published more than 30 years ago. During the last 25 years several

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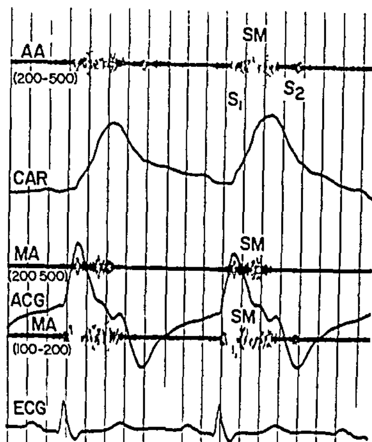


Fig 1 Phonocardiogram with apexcardiogram and external carotid pulse tracing in patient No 4 showing a crescendo-decrescendo systolic murmur at the aortic area *(AA)* and a slightly different systolic murmur at the mitral area *(MA)* *ECG* electrocardiogram *ACG* apexcardiogram *CAR* external carotid artery pulse tracing *S* first heart sound *S* second heart sound *SM* systolic murmur the numbers *(200 500) (100 200)* refer to frequency cycles per second (Hz)

excellent accounts[5, 8] of the gross and microscopic findings in this entity have included some clinical correlations especially with respect to associated cardiac murmurs The salient and clinically relevant pathophysiologic features of MAC include

1 MAC of minor degree consisting merely of specks or small nodules of calcium, usually under the posterior mitral cusp causes no significant distortion of mitral-left ventricular anatomy It is of little or no importance [11]

2 In moderate degrees of MAC calcific deposits are larger and perhaps confluent but do not encompass the whole mitral ring They are situated mainly below the posterior mitral cusp which thereby is distorted and displaced upward towards the left atrium in half the cases

3 In patients with severe or massive MAC a rigid curved bar or ring of calcium 1 to 3 cm in cross sectional diameter encircles all or most of the mitral orifice Calcific spurs may project varying distances into the adjacent left ventricular myocardium and often into the membranous ventricular septum in the vicinity of the His bundle and its branches The main mass of MAC protrudes beneath the mitral cusps and may be densely adherent to them because it projects towards the left atrial aspect of the mitral orifice the bulky bar or ring of MAC elevates and immobilizes the basal two thirds or more of the mitral leaflets permitting only a small portion of each leaflet, near its free edge to move freely during diastole [8] Sometimes the elevation and atrial (upward) displacement of the mitral cusps especially the posterior one are so extreme that the cusps and their chordae tendineae are stretched taut thereby preventing both normal diastolic excursions and systolic coaptation

4 Immobilization of the mitral valve and its chordae due to mechanical stretching by a massive bar of MAC is one cause of mitral regurgitation The other cause of mitral incompetence in patients with MAC is loss of the normal systolic contraction (sphincter action) of the mitral ring[13] resulting from the splinting effect of the rigid annular calcification

5 Mitral stenosis resulting from MAC is much rarer than mitral regurgitation and probably is never of severe degree Narrowing of the mitral orifice may occur when severe MAC encroaches on or protrudes into it Additionally the diastolic flow of blood across the mitral valve may become impeded when extensive adherence develops between the ventricular surface of the mitral cusps and the MAC, with the resultant formation of an immobile rigid shelf[5, 7] Although such distortion of the anatomy of the mitral apparatus does not progress to the point of critical mitral stenosis it may in some instances cause sufficient turbulence to produce apical diastolic murmurs

6 Occasionally secondary or complicating pathologic changes have been observed in MAC (a) thick fibrous or fleshy encapsulation of the calcified bar (b) central caseation in the MAC forming a pocket of thick pultaceous material[8, 11] (c) ulceration or extrusion of calcium through a mitral cusp into the left atrial cavity (d) bacterial endocarditis and (e) large pedunculated myxoid thrombi originating on an ulcerated MAC with systemic embolism[1]

7 Calcification in the aortic valve cusps has been a frequent associated finding in all series and is present in from 25 per cent to 74 per cent of the reported cases [11] These calcific deposits occur in the fibrous portion of the valve cusps but not in



Fig 2A Posteroanterior chest roentgenogram of Patient No 4 a 3 year old woman showing calcification in mitral annulus as well as aortic root areas *(arrows)* *Fig 2B* Same patient as in *Figs 1* and *8*



Fig 2B Lateral chest roentgenogram of Patient No 4 a 3-year-old woman For details see legend to *Fig 2A*

the fibrous annulus of the aortic valve Unlike secondary calcification in rheumatic or congenital aortic stenosis usually no fusion of the aortic cusps at their commissures is observed Nevertheless the aortic valve calcification in patients with MAC can sometimes be so heavy and extensive that hemodynamically significant aortic stenosis is produced Whether significant stenosis is present or not the projecting calcific masses in the aortic cusps may produce turbulent systolic flow in the aortic root and consequently a harsh systolic murmur conducted into the carotid arteries may be heard

Clinical features

Evidence of congestive heart failure is seen frequently in association with MAC Heart failure was present in 53 per cent of Pomerance's patients with MAC but other cardiac pathology was at least partly responsible in all but 3 per cent In an autopsy study of 370 patients over 75 years of age MAC was encountered in 35 per cent of those who had been in heart failure and in 22 5 per cent of those without heart failure Twelve of Korn s 14 patients with massive MAC were in congestive failure at the time of death Most reports suggest that MAC plays a contributory rather than a primary role in the genesis of heart failure either by (a) producing or aggravating mitral regurgitation (b) leading to A V block or (c) possibly distorting left ventricular geometry and thereby interfering with the mechanics of ventricular systole

A loud harsh systolic murmur best heard at the left lower sternal edge or at the apex is the commonest abnormal clinical finding in all series The association of such a murmur with MAC was mentioned in 1935 by Libman and later was described in detail Retrospective scrutiny of clinical data in patients with MAC proved by autopsy reveals that from 35 per cent to 100 per cent of these patients had systolic murmurs - Systolic murmurs were three times more common when severe MAC distorted the posterior mitral cusps than when MAC was slight or moderate and without mitral valve distortion In a study of the postmortem findings in 173 patients over 70 years of age in whom systolic murmurs had been

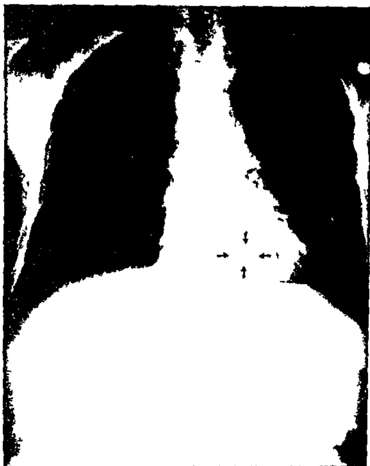


Fig 3A Posteroanterior chest roentgenogram of Patient No 2 a 72 year old man demonstrating a large nodule of calcification in the region of the posterior mitral annulus *(black arrows)* This patient s echocardiogram is shown in *Fig 6*



Fig 3B Lateral chest roentgenogram of Patient No 2 a 72 year old man There is calcification in the aortic valve area *(white arrow)* For details see legend to *Fig 3A*

observed during life, 70 (41 per cent) had MAC as the sole or predominant cardiac lesion[1] The apical or left parasternal systolic murmur in patients with MAC is usually attributed to mitral regurgitation although Geill[1] suggested it could be due to vibration of the calcified mitral ring itself If aortic valve sclerosis or calcification is also present as is often the case systolic ejection murmurs originating at the aortic valve may conduct downwards to the vicinity of the apex in actual clinical practice it is often difficult in patients with known MAC to make a definite distinction between such a transmitted aortic murmur and a murmur that is due to mitral regurgitation (Fig 1)

On the other hand diastolic murmurs caused by MAC are rare They were heard in only five of 59 patients of Simon and Liu[5] and three of Korn and colleagues patients[7] Rytand and Lipsitch[18] recorded diastolic murmurs related to atrial contraction in four of their five patients with complete A V block and MAC

Cardiac conduction defects are caused by encroachment of MAC or its projections into the ventricular septum where the His bundle and its branches are vulnerable[13] Complete A V block was described in a patient with MAC as early as 1908 by Bonniger and several other case reports followed[1, 7] Five of the ten patients of Rytand and Lipsitch[18] had this complication, but only one of 14 of the patients of Korn and associates and one of 25 studied by electrocardiography by Pomerance showed complete A V block Four of the patients of Korn and associates and nine of Pomerance showed bundle branch block Atrial fibrillation was present in nine patients and a bizarre supraventricular tachycardia in one patient in the series of Korn and associates Of Geill s five patients in whom calcium offshoots of MAC invaded the ventricular septum two had complete A V block two had bundle branch block and one presented with ventricular tachycardia Atrioventricular or intraventricular conduction defects occurred in 52 per cent of our 38 patients with MAC However when the incidence of various types of conduction abnormalities in these patients was compared to the incidence in 300 patients without MAC (on echocardiography)

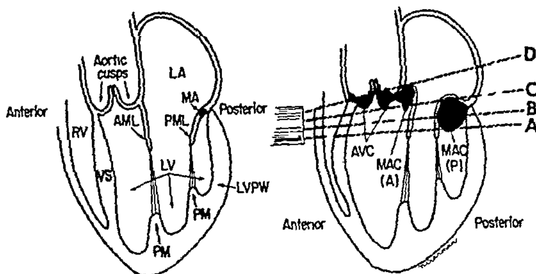


Fig 4 Diagrammatic cross section of the heart in normal individuals *(left)* and those with MAC *(right)* The latter depicts the anatomical relationships of calcification *(solid black areas)* in the posterior and anterior mitral annulus, and in the aortic root and the manner in which the ultrasound beam transects them in various transducer directions *RV* right ventricle *LV* left ventricle *VS* ventricular septum *LVPW* left ventricular posterior wall *PM* papillary muscle *AML* anterior mitral leaflet *PML* posterior mitral leaflet *LA* left atrium *MA* mitral annulus *AVC* aortic valve cusp *MAC(A)* anterior mitral annulus calcification *MAC(P)* posterior mitral annulus calcification

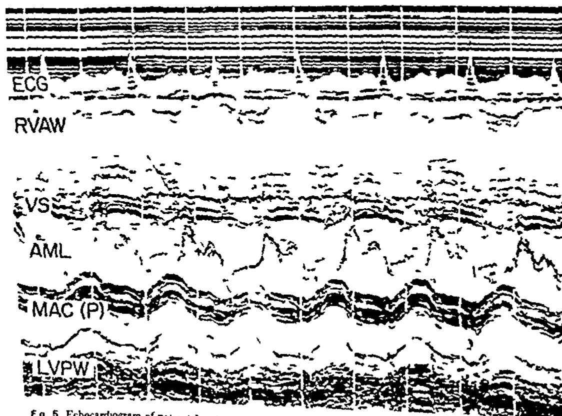


Fig 5 Echocardiogram of patient No 1 a 69 year-old woman showing posterior MAC that has displaced the mitral valve to an unduly anterior position within the left ventricular chamber *ECG* electrocardiogram *RVAW* right ventricular anterior wall

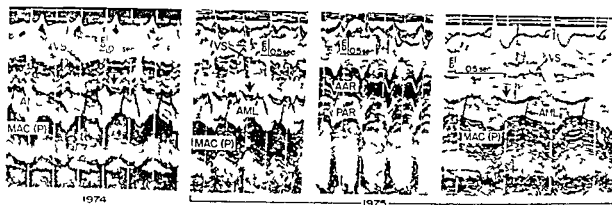


Fig 6 Echocardiogram of patient No 2 a 72 year old man with massive posterior MAC which increased in extent from August 1974 to July 1975 *The arrows in the first second* and *fourth panels* indicate a dense linear or band like echo that moves parallel to the ventricular septum This echo possibly may originate in calcium in the aortic cusps or aortic annulus *The third panel* shows dense calcification in the aortic root *AAR* anterior aortic root *PAR* posterior aortic root

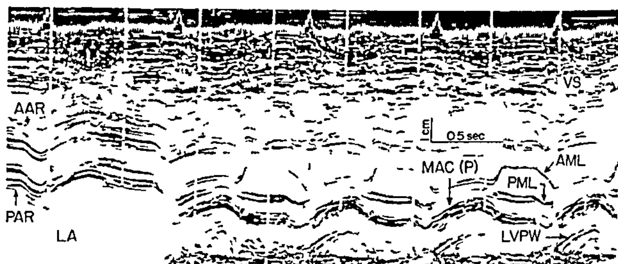


Fig 7 Echocardiogram of patient No 3 a 75 year old woman with posterior MAC that is suggestive of mitral stenosis See text for discussion

of the same age range only right bundle branch block occurred significantly (p < 02) more often in the group with MAC

The roentgenographic detection of MAC was described three decades ago by Sosman [4] de Oliveira [5] and Roesler [5] Oblique projections are more effective in demonstrating MAC than the posteroanterior one fluoroscopy cinefluorography and tomography are superior to conventional chest roentgenograms for this purpose MAC is visualized in several cases as an annular J shaped or U shaped density [6] within the cardiac silhouette in its lower posterior portion (Fig 2) but in other instances only linear nodular or specks of calcification may be discerned in the region of the posterior mitral annulus (Fig 3)

Echocardiographic features

The detection by ultrasound of calcification in the region of the posterior mitral annulus has been reported recently [1] and several brief communications in abstract form confirm that echocardiography is a sensitive means of detecting MAC probably superior in this respect to radiologic techniques [1] We have studied the echocardiograms of 38 individuals with MAC The youngest was 63 years and the oldest 90 years 12 were men and 26 were women A Picker Echoview 10 Ultrasonoscope was used and was connected to a Honeywell 1856 stripchart recorder In our initial ten patients [11] we required radiographic or cinefluorographic confirmation of MAC It soon became apparent to us however and also to others that the echocardiographic appearances of posterior MAC were characteristic were seen in all cases in which MAC was observed radiologically and were probably a more sensitive and reliable indicator of MAC than roentgenographic studies In our last 25 patients therefore we have not insisted on radiologic confirmation of MAC if the echocardio

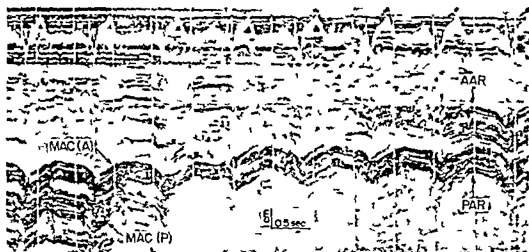


Fig 8 Echocardiogram of patient No 4 a 3 year old woman with both posterior and anterior MAC The echo of posterior MAC ends abruptly as the scan is continued to the aortic root but the echo of anterior MAC becomes continuous with calcification in the region of the posterior aortic root The mitral cusps are not visible because of the low gain setting and also perhaps because of the obscuring effect of the anterior MAC

graphic features of posterior MAC were unequivocal

We shall describe the variety of patterns that MAC can produce depending upon (1) whether MAC involves only the posterior portion of the annulus or both posterior and anterior portions of the annulus and (2) whether the ultrasound beam transects the mitral apparatus at high middle or low levels

In addition we shall illustrate the fact that distortion of the normal anatomy of the mitral apparatus by severe MAC results in abnormalities of mitral valve motion and position that can mimic mitral stenosis hypertrophic cardiomyopathy and pericardial effusion

Interpretation of the echocardiogram in MAC is facilitated by consideration of a diagrammatic section of the heart (Fig 4) which is based on published pathologic descriptions A schematic diagram of the normal heart is shown on the left The mitral valve annulus which does not quite encircle the base of the valve is shown posteriorly but not anteriorly The diagram to the right depicts extensive calcification of the mitral ring as well as of the aortic valve

Depending on the orientation of the transducer one can produce several different echocardiographic patterns (Fig 4 *right*) Thus projections A and B produce echoes of the septum the anterior mitral leaflet the thick posterior calcified mitral annulus sometimes a narrow open space (in projection A) and the left ventricular posterior wall Sound beamed in direction C results in echoes of the septum calcification if present in the aortic valve or the region of the aortic ring perhaps anterior mitral leaflet and posterior mitral annulus calcification A transducer pointed more cephalad in direction D reveals either a normal or calcified aortic root and cusps

In our series echocardiography of the LV revealed MAC as a dense echo 3 to 22 mm (average 9 mm) in width situated anterior to the LV posterior wall and moving parallel to it The mitral valve leaflets *were often* displaced to a relatively anterior position within the LV by the bulky mass of calcific material protruding into the LV behind the attachment of the posterior mitral cusp (Figs 5 and 6) In 29 patients the posterior mitral cusp could be identified easily with a narrow sonolucent space between it and the MAC in the other nine patients the posterior mitral cusp was obscured by and indistinguishable from the dense echo of posterior MAC

The diastolic anterior excursion of the anterior mitral leaflet was often abnormally small as were the E F slope and the maximum separation of the mitral cusps (Table I) The latter measurement could be made only in those 29 *patients in* whom both mitral cusps could be visualized adequately in all these patients the posterior mitral cusp showed diastolic motion of the normal posterior type The mitral cusps did not appear thickened or calcified in any *of the* 38 patients The patients with the thickest posterior MAC tended to show the smallest diastolic mitral excursions and

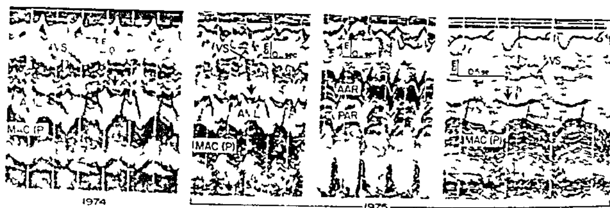


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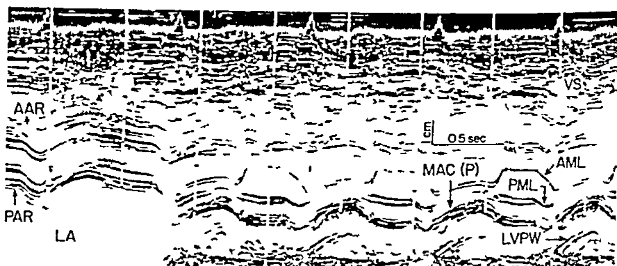


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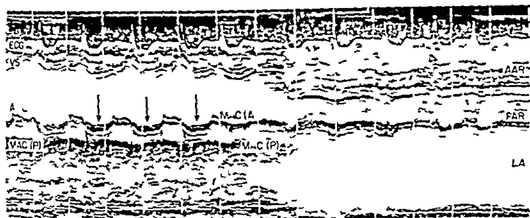


Fig 9B Echocardiogram of same patient as in Fig 9A Scan from LV to aortic root For discussion see text



Fig 10 Echocardiogram of patient No 6 a ? year-old woman showing posterior MAC as well as anterior MAC See text for discussion

Patient No 3 In another patient (Fig 7) the posterior MAC is seen well and the anterior mitral leaflet has a low E F slope a feature present in 75 per cent of this group of patients The posterior leaflet however moves posteriorly in diastole suggesting that true mitral stenosis probably is not present

Patient No 4 The ultrasound beam transecting the base of the mitral valve ring (Fig 8) produces echos of thick calcification of the anterior ring as well as the posterior ring A scan to the aorta shows the continuity between the anterior mitral ring calcification and the posterior aortic root

Patient No 5 Figs 9A and B are segments of the echocardiogram of a woman with calcific aortic stenosis In Fig 9A the anterior mitral leaflet is visualized clearly anterior to the dense echo of posterior MAC in the first beat and the last three beats During the intervening beats a slight shift in transducer direction brings another dense echo of anterior MAC *(arrows)* into view which partly obscures the anterior mitral leaflet Fig 9B demonstrates a scan from LV to aortic root The posterior MAC disappears abruptly as the aortic root and left atrium are visualized A transition is apparent from anterior mitral leaflet *(first beat)* to anterior MAC *(arrows)* which overlaps the anterior mitral cusp and which then becomes continuous with the posterior aortic root

Patient No 6 Fig 10 is from the echocardiogram of a woman with a harsh systolic murmur audible at apex as well as base MAC is present posteriorly *(MAC(P))* as well as anteriorly *(MAC(A))* The anterior MAC together with the anterior mitral leaflet is continuous with the posterior aortic root whereas the posterior MAC ends abruptly as the transducer beam shifts from the left ventricle to the left atrium *The upper set of three vertical arrows* indicates a linear or band like echo between the ventricular septum and the

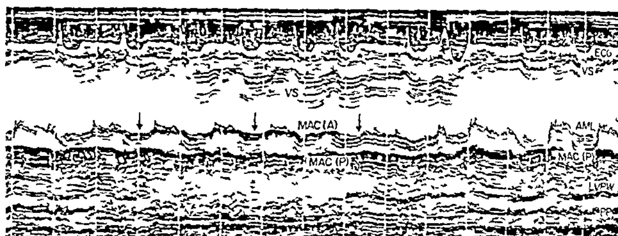


Fig 9A Echocardiogram of patient No 5 a 75 year old woman with both posterior and anterior MAC For discussion see text

Table I Characteristics of diastolic mitral valve motion in 38 patients with mitral annulus calcification

	Range	*Number of patients*
E F slope of anterior leaflet (mm /sec)	10 20	6 (16%)
	21 30	12 (32%)
	31 40	10 (26%)
	over 40	10 (26%)
Diastolic anterior excursion of anterior mitral leaflet (mm)	5 10	5 (13%)
	11 15	13 (34%)
	16 20	16 (42%)
	over 20	4 (11%)
Total diastolic separation of mitral cusps (mm) (29 patients)	11 15	3 (10%)
	16 20	9 (31%)
	21 25	12 (41%)
	over 25	5 (18%)

mitral E F slopes whereas those with the narrowest posterior MAC usually exhibited mitral diastolic excursions and mitral E F slopes that were either normal or in the borderline low range

In addition to posterior MAC located at or just behind the level or plane of the posterior mitral cusp we also observed in seven patients anterior MAC at the level or plane of the anterior mitral cusp Scans done from the LV to aortic root revealed that posterior MAC ends abruptly whereas anterior MAC together with the anterior mitral leaflet becomes continuous with the posterior aortic root (Figs 8 and 9)

In eight patients with posterior MAC a linear or bandlike dense echo (Figs 6 and 10) was observed in the LV outflow region (between the ventricular septum and the anterior mitral leaflet) that moved in the same direction as the septum during systole and diastole All these patients revealed probable calcification in the aortic root on echocardiography The precise nature of this abnormal echo in the LV outflow tract remains uncertain but it probably originates either in calcific deposits in the aortic cusps which protrude downward into the uppermost (subaortic) portion of the LV chamber, or in calcific deposits in the region of the aortic annulus

Patient No 1 The anterior mitral leaflet appears more anterior than normal (Fig 5) apparently as a result of being pushed forward by a thick calcified mitral annulus Posterior to the MAC is the left ventricular posterior wall The *distinction between these two structures* is important in order not to make the erroneous diagnosis of pericardial effusion [4]

Patient No 2 This patient s echocardiogram (Fig 6) from 1974 shows *(from anterior to posterior)* the ventricular septum anterior calcification of the mitral ring or calcification in an aortic cusp *(heavy arrow)*, the anterior mitral leaflet posterior calcification of the mitral annulus and the left ventricular posterior wall By 1975 the posterior MAC has become thicker and the anterior and posterior aortic root are heavily calcified

It might appear that the septum and anterior mitral ring *(heavy arrow in first second and fourth panels)* are really only the two sides of a thick septum but the last tracing taken at a faster paper speed and decreased amplification clearly shows the two sides of a ventricular septum of normal thickness

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anterior mitral leaflet which becomes continuous with the aortic valve echo as the scan is continued to the aortic root It seems likely that this linear echo in the left ventricular outflow tract originates in calcific deposits in the aortic valve or aortic annulus that protrude downward into the subaortic region The ultrasound beam thus transects in succession the ventricular septum calcification in the aortic valve area anterior MAC with *anterior mitral leaflet* posterior mitral leaflet posterior MAC and left ventricular posterior wall (Fig 4 *right projection* C) The identity of the ventricular septal echo is established by its continuity with the anterior aortic root echo

Excluded from the above series were seven patients with MAC under the age of 60 years Two of them aged 37 and 53 years had associated mitral stenosis which was confirmed at autopsy in one and at open heart operation in the other The other four patients aged 23 29 32 and 57 years were all in chronic renal failure and had had hemodialysis

Importance of the recognition of MAC in clinical echocardiography

Non invasive assessment of the presence and extent of MAC and of its mechanical effects on mitral valve anatomy and motion appears to be possible by echocardiography All of our studies showed posterior mitral ring calcification sometimes massive accounting for an abnormal anterior position of the mitral valve (Figs 5 and 6) Some of our patients also had anterior MAC, which is much less common than posterior MAC and is easily overlooked (Fig 9A) Calcification in the aortic cusps or in the region of the aortic annulus where it is contiguous with the mitral annulus may protrude downward into the left ventricular outflow tract (Fig 4 *right*) The linear or band like echo arising from such calcium deposits is situated between the ventricular septum and anterior mitral cusp and may resemble the left border of the ventricular septum Thus an echocardiographic picture similar to IHSS may result (Figs 6 and 10) This diagnosis may be excluded however by demonstration of the echoes of both sides of a septum that is of normal thickness (Figs 6 and 10) which becomes continuous with the anterior aortic root (Fig 10)

The E F slope of the anterior mitral valve leaflet was decreased in most of our patients (Figs 6 7 and 9) This *finding can be differen*tiated from true mitral stenosis by the normal direction of the diastolic movement of the posterior mitral leaflet Although the diastolic closure rate of the normal mitral valve is related to the rate of left ventricular filling [1] other factors may play a role in determining the E F slope in the presence of an abnormal mitral valve apparatus [22] The diastolic movement of the anterior mitral leaflet is frequently abnormal in the presence of MAC The restriction to opening and impairment of closure produced by massive MAC may be the result of several factors including stretching taut of the mitral cusps and chordae intimate involvement with calcification of the bases of the leaflets and loss of the effect of the normal vortex produced behind the mitral leaflets by inrushing blood [1,3] because these currents are now blocked by protuberant calcified masses

The dense well defined echo of posterior MAC may appear, by suitable gain adjustment to be separated from the pericardial or epicardial echo by an echo free space that may be interpreted as a pericardial effusion if the calcified mass is mistaken for left ventricular posterior wall [1] Accumulation of fluid in the pericardium may be ruled out however by scanning from the left ventricle to the aortic root echoes of the calcified posterior annulus terminate abruptly with sweep to the left atrium [1] whereas the true left ventricular posterior wall echoes disappear gradually with such a sweep

Awareness of the echocardiographic patterns of MAC allows this entity to be differentiated from pericardial effusion mitral stenosis and IHSS Such awareness provides an approach to the understanding of the abnormalities of mitral valve motion produced by calcification of the mitral ring Moreover the pathophysiologic abnormalities produced by MAC provide a possible etiologic basis for syndromes characterized by heart failure systolic and/or diastolic murmurs and various types of bundle branch and intraventricular conduction defects

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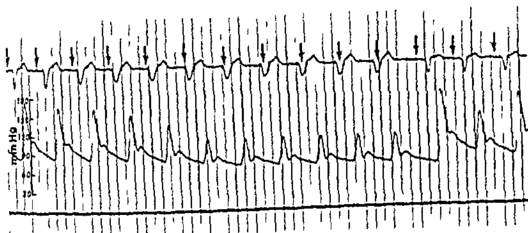


Fig 1 A patient with severe symptoms of dizziness during normal pacing *In the upper ECG* the arrow marks the position of the P wave When the P wave precedes the QRS in the usual physiologic sequence the peripheral arterial pressure is as high as 180/90 mm Hg When the P wave (and atrial systole) occurred during the ventricular QRS the pressure fell to 110/80 mm Hg Despite the continuance of the loss of the physiologic sequence the symptoms stopped spontaneously several weeks later

pacer artifact [3] Intermittent loss of stimulation especially coupled with intermittent decrease of stimulus artifact amplitude suggests lead disruption (Fig 3) Intermittent ventricular pacing with a normal amplitude (though not the usual stimulus vector) stimulus artifact suggests the physical integrity of the lead and that it is displaced or that threshold of stimulation has risen above the pacer output Holter monitor recording or continuous recording in a monitored unit is also valuable

The electrocardiogram and other non invasive tests can often yield additional valuable data

X ray Unequivocal displacement of the lead within the heart (Fig 4) lifting of the infected myocardial electrodes from the surface of the heart (Fig 5) or visualization of a fractured intramyocardial lead (Fig 6) will diagnose the cause of the difficulty and indicate the required repair

An even more sensitive indicator of the integrity of the lead-connector system is the display of the pulse generator stimulus on an oscilloscope Display of the artifact at a rapid sweep and with appropriately sensitive equipment will show a change from the normal output of the pulse generator and unequivocally indicate lead disruption whether or not fracture of the conductive element or insulation is visible on x ray (Fig. 7)

Such a display will also indicate in one of two ways whether depletion of the power source has occurred The artifact may decrease in amplitude compared to an earlier recording or the impulse duration may increase (Medtronic pulse generators) from that set at manufacture (Fig 8) In the former the shape of the artifact will remain identical though lower in over all amplitude In the latter the shape will be similar, though of greater duration In both situations the artifact

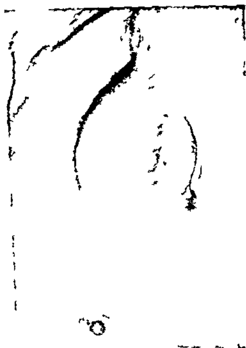


Fig 2 This pacemaker implanted superficially in the anterior axillary line gradually thinned the overlying skin As infection was not present wound revision movement of the pacemaker medially and development of a generous skin flap was adequate to stop impending wound breakdown

Cardiac pacing and pacemakers VI Analysis of pacemaker malfunction

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Bronx N Y

Implantation of a cardiac pacemaker represents the application of electrical and mechanical engineering principles to medicine Failure of the relationship may be analyzed by comprehension of the physiologic and bioengineering principles involved Malfunction of the electronic and mechanical factors must be clearly and distinctly separated from physiologic problems and from normal function of both, but a poor interrelationship Rational management is dependent on proper investigation and interpretation of the malfunction The correct techniques of investigation are critical to comprehension of the problem

1 History A careful history of the return of symptomatology is required Is the symptom that has returned identical to that which caused initial pacemaker implant or is the symptom new and different? The return of syncope implies intermittent or lost cardiac capture the development of rhythmic waves of weakness suggestive of orthostatic hypotension may suggest the pacemaker syndrome [1] The complaint of palpitations, presumes atrial or ventricular premature contractions, which may be spontaneous or pacemaker induced

The *first* symptom suggests intermittent capture following lead fracture reduction in pacer output threshold rise above the output capability of the pulse generator electrode displacement or ventricular perforation The *second* suggests the possibility that the atrial contribution is required to maintain cardiac output and that as the atrial P waves move into the QRS complex cardiac output and peripheral pressure fall symptomatically (Fig 1) The *third*, palpitations may indicate the loss of adequate sensing and competitive pacer rhythms

2 Physical diagnosis The presence of an implantable pacemaker should cause no local pain If pain exists, the pacer skin pocket may be too tight or the wound may be infected with a rapidly growing *(staphylococcus aureus)* or slow growing *(staphylococcus epidermitis)* organism An uninfected wound may be on the verge of or actually broken down because of pressure necrosis of the skin wound decubitus or the pacer may be in a skin fold and cause discomfort A pulse generator in the axilla or in the anterior axillary fold will rub against the arm with each movement and cause severe discomfort Only examination of the patient will permit this determination (Fig 2)

An infected wound requires removal of the system and reimplantation elsewhere A tight wound requires revision and culture to be certain that it is clean A painful wound should be revised If the generator is in a sensitive area it should be removed and reimplanted

Attention to physical diagnosis coupled with laboratory diagnosis is important A patient who complains of return of symptoms may have no physical findings

3 Presentation with findings suggestive of loss of pacing may cause severe diagnostic problems A long electrocardiogram should be performed in a lead which clearly shows the pacemaker artifact If intermittent cardiac stimulation is recorded the diagnostic problem of the cause of symptoms will be resolved The cause of the intermittent pacing still remains to be determined

The ECG may indicate the likelihood of lead disruption by change in electrocardiographic appearance or the direction of the vector of the

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immediate revision and development of an adequate flap will resolve the problem Once the skin is broken and the pacer exposed it must be presumed to be infected A dry non purulent wound breakdown may nevertheless be salvaged by development of a new flap and irrigation for several days with bactericidal antibiotic solution If purulent the organism is of paramount importance[7] Staphylococci cannot be treated with antibiotic irrigation and no effort need be made Escherichia coli or streptococcus infection is amenable to parenteral and local antibiotics and revision and antibiotic therapy may be attempted[8] If the patient is febrile and blood cultures are positive all hardware should be removed intravenous antibiotic therapy should be begun and be continued for several weeks after the patient is no longer febrile and blood cultures are negative New hardware should be implanted at a fresh site during antibiotic administration

The operation

Once preoperative evaluation of a patient s status has been completed operative intervention is required to replace a defective generator repair or replace a defective lead replace an intact pulse generator with one more suited to the patient replace or abandon a defective lead or replace or abandon an intact lead placed in a poor position The satisfactory correction of a malfunction depends on the rational analysis of the problem In order to achieve this rational analysis intraoperative data is required

X ray may have already shown a clear cut lead displacement and the need for its replacement in the proper cardiac position A lead fracture visible on plain film or cine film in which an apparently intact lead is seen to separate with movement will indicate repair Even a poor connection can be found on preoperative x ray (Fig 9) If the fracture is accessible repair can be undertaken If fracture is within the venous system intrathoracic or intramyocardial repair will be unsatisfactory or impossible and a new lead should be placed If the fractured lead is irreparable and uninfected it may be abandoned If the lead is infected it must be removed and if it is also trapped traction or even cardiopulmonary bypass will be required

Operative evaluation of the lead system and pulse generator involves inspection for the integrity of the conductive element and insulation the adequacy of connection between lead and pulse generator wound culture and biopsy if infection is suspected and test of the function of the lead system and pulse generator As each pulse generator is designated by manufacturer model and serial number its operational characteristics can be determined from the manufacturer s literature The electrode system too has specific operational characteristics which can be compared to intraoperatively determined data The intraoperative ability to analyze actual function of the equipment involved is required

Fig 5 Myocardial electrodes with a high threshold The two are lifted out of the ventricular wall and lie in a soft tissue mass adjacent to the ventricle During thoracotomy this was found to be a purulent coagulum

Pulse generator output pulse duration and sensitivity (if applicable) should be tested The lead system should be tested for four factors from which the variety of malfunction of the lead system can be ascertained (Table I) The *voltage* and *current* thresholds of stimulation the *impedance* to electrical flow and the amplitude and slew rate or frequency of the *cardiac electrogram* Each factor may vary independently of the other (see Cardiac Pacing and Pacemakers sections II and IV)

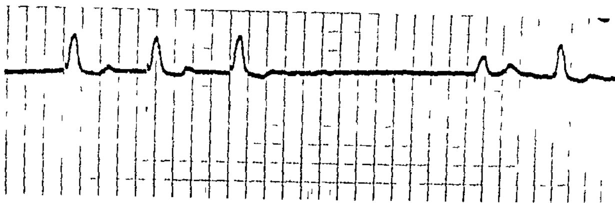


Fig 3 The changing amplitude of the artifact with loss of ventricular capture is virtually pathognomonic of lead disruption



Fig 4 The electrode is displaced from the ventricular apex to the outflow tract Threshold was variable and high Despite a high output pulse generator intermittent capture occurred

will resemble earlier artifacts which were clearly normal Lead disruption produces a distorted artifact (Fig 7)

The coupling of provocative maneuvers with electronic analysis of pacemaker function and electrocardiography is the most sensitive non invasive indicator of malfunction If physical examination and ECG including Holter monitoring do not unmask failure to pace or sense the patient should be connected to the ECG and the oscilloscope for electronic analysis of the generator artifact He should be turned side to side made to lie down stand up bend straighten and the pulse generator and electrode should be manipulated in the subcutaneous tissue These maneuvers may distract the elements of a partially disrupted lead or connector and lose pacing and/or sensing and produce the typical changes in the oscilloscopic display of the pacer stimulus

Operative management of pacer malfunction

Whenever findings of intermittent or absent pacing or clear cut lead disruption exist revision of the pacer system is required Intermittent sensing is a less serious problem and the surgeon should evaluate whether the loss of sensing is sufficiently severe and whether runs of pacer induced tachycardia or prolonged asystolic pauses exist to require revision Occasional and moderate sensing failure may be treated expectantly

Wound decubitus and infection

The management of wound decubitus requires a degree of urgency A wound which is too small for the pacer with skin which is tight and thinned (perhaps with the pacer visible through the skin) requires immediate intervention As long as the skin is intact (though thinned) it will be a barrier to infection the pacer sac will be clean and

The following clinical examples may serve to illustrate the possibilities of intraoperative analysis

Case reports

Case 1 Patient M M (female) with sick sinus syndrome underwent implantation of a bipolar pacemaker via the subxiphoid transmediastinal route The two Medtronic 6917 electrodes were implanted on the diaphragmatic surface of the right ventricle with a bipolar Medtronic 5950 pulse generator following three previous unsuccessful attempts at transvenous pacemaker implant On the third postoperative day intermittent sensing was found She was transferred to Montefiore Hospital and Medical Center for revision

On exposure of the lead system the 1 0 msec stimulation threshold was 0 58 milliamperes and 1 04 volts the impedance 400 ohms The impedance is a function of the pulse duration and the output of the measuring device as well as the usual electrical resistance In our laboratory impedance is measured with a rectangular pulse and a constant current output of 10 0 milliamperes at a 1 0 msec pulse duration At threshold the impedance is different It is important that each measurement be done under the same circumstances so that the data is comparable The bipolar electrogram QRS amplitude was 4 mV and the slew rate was 2 1 volts/second The total amplitude was too small to trigger a pulse generator Each lead separately had a QRS amplitude of 3 0 mV and a slew rate of 0 84 volt/second Both were within the output (for pacing) and sensing capability of a high sensitivity pulse generator (though not one of normal sensitivity) designed for sensing atrial activity The unipolar generator Biotronik† IDP 64 was attached to one lead the other was abandoned Pacing and sensing have remained normal The problem was that of two small unipolar and a small bipolar signal The resolution was the use of a high sensitivity pulse generator

Case 2 Patient R K with intermittent heart block underwent implantation of a Medtronic 6901 bipolar electrode and a Medtronic 5950 pulse generator One month later intermittent sensing was found The threshold of stimulation at 1 0 msec was 1 4 mA and 0 78 volts the impedance 550 ohms The bipolar electrogram amplitude was 3 5 millivolts and the slew rate was 0 5 volts/second The electrogram from the electrode tip had an amplitude of 15 0 millivolts and a slew rate of 1 73 volts/second thus the unipolar electrogram was satisfactory the bipolar poor The problem was resolved by conversion of the electrode to a unipolar system using the same pulse generator and electrode Pacing and sensing have remained normal The problem was that of a small bipolar signal made up of two larger unipolar signals The proper resolution was to unipolarize the electrode

Case 3 Patient W S with complete heart block had had a bipolar Medtronic 6901 electrode implanted with a CPI‡ 401 bipolar pulse generator both in place for two years Intermittent pacing with syncope occurred There were no helpful radiographic findings At operation thresholds of stimulation were determined The electrode tip had a 1 msec stimulation threshold of 1 7 milliamperes and 5 46 volts (the latter above

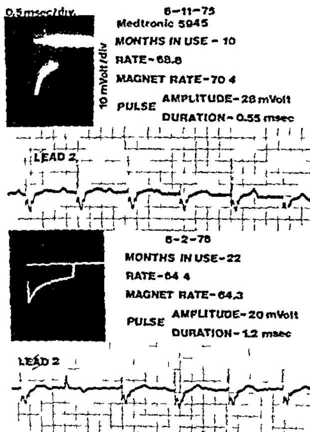


Fig 8 Medtronic pulse generators increase pulse duration as battery voltage declines Despite normal pacing and sensing the rate decline and increase of pulse duration clearly indicates battery depletion

the output capability of the generator) The electrode impedance was 4 300 ohms, indicative of a lead fracture in this instance invisible on x ray In the voltage test made the generator increases its current output until the indicated output voltage is reached In the current test made the voltage is increased until the indicated current output is reached As the two processes are not visible voltage and current must be measured separately The 1 msec stimulation threshold of the proximal or ring electrode was 5 9 milliamperes and 2 45 volts and impedance of 400 ohms well within the output capability of a conventional output pulse generator A unipolar Cordis§ 190L pacemaker was attached to the proximal terminal It was set at 70 per minute and an output of *high* (4 5 volts at 1 7 msec) The threshold was at a rate of 90 and an output of medium (3 0 volts at 1 4 msec) (see Cardiac Pacing and Pacemakers section V) As the threshold was chronic and stable this was deemed a satisfactory margin Pacing has remained satisfactory This circumstance was that of an occult lead fracture detected by high impedance and corrected by using the demonstrably satisfactory lead of a bipolar system.

Case 4 Patient J L with complete heart block had had

Medtronic Inc Minneapolis Minn
†Biotronik Sales Inc St Petersburg Fla
‡Cardiac Pacemakers Inc St Paul Minn

§Cordis Corporation Miami, Fla



Fig 6 Intermittent pacing was investigated by chest x ray Two electrode fractures were found within the myocardium Repair is impossible A new electrode system is required

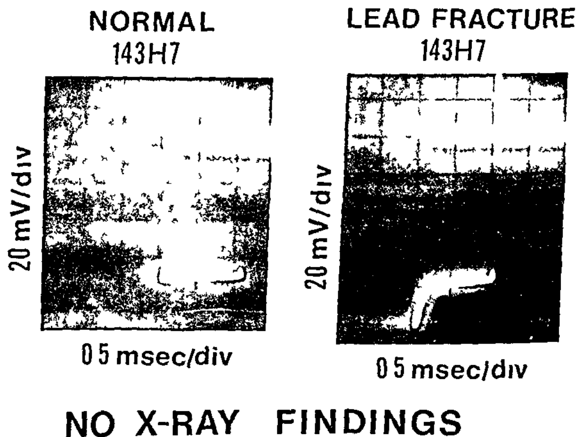


Fig 7 The markedly distorted artifact from an earlier *(left)* to later *(right)* stimulus artifact clearly indicated lead disruption as a cause for intermittent pacing though no x ray findings existed



Fig 10 Four electrodes two bipolar sets both unsuccessful had been implanted One electrode of each pair had a high but workable threshold Revision consisted of determining which of the electrodes were satisfactory and then conversion to unipolar pacing

In this instance neither electrode was usable both were insulated and abandoned in the subcutaneous tissue Transvenous implant was again attempted Because of the difficulty in holding an intracardiac position a Biotronik IVE 185 electrode with hooks for attachment to the endocardium was used. The electrode position has been stable and pacing and sensing satisfactory In this instance it was important to recognize the need for an actively attaching electrode rather than one which attaches passively to the right ventricular endocardium (see Cardiac Pacing and Pacemakers section V)

Case 7 Patient H R had had two unsuccessful attempts at transvenous implant He then underwent left anterolateral thoracotomy implant with both Medtronic 6913 electrodes in the left ventricle Threshold rose stimulation stopped and the pulse generator was replaced by a high output model Medtronic 5990 When pacing became intermittent again the patient was referred for revision The wound was opened cultured and the leads detached from the pulse generator The impedance of each electrode was 400 ohms (normal) Current threshold was 16 1 milliamperes and 6 4 volts and 17 1 milliamperes and 6 8 volts respectively at 1 msec pulse duration The thresholds were above the output of even a high output pacemaker but more important culture grew *staphylococcus epidermidis* indicating the probability of infection at the myocardial level The electrodes were insulated and abandoned and the wound was drained At no time did the patient give evidence of intrathoracic or systemic sepsis (Fig 5)

Transvenous implant was performed with a Medtronic bipolar electrode and an output variable Medtronic 5961 pulse generator (output 5 4 volt pulse duration noninvasively variable from 0 05 to 1 msec current limited at 10 to 11 mA) Implant was difficult but eventually a 1 msec stimulation threshold of 0 6 mA was found As the earlier implant had used generators of similar output with pulse duration fixed at 0 5 msec the 5961 pulse generator allowed greater pulse duration and therefore output if necessary and noninvasive measurement of threshold

Post implant threshold rose slowly reaching a maximum at a pulse duration of 0 6 msec six weeks after implant As pulse duration was never left below 1 5 msec the patient continued to pace at all times

Stabilization of threshold occurred and then declined to a pulse duration of 0 20 msec where it has remained for 1 years Pulse duration for prolonged stimulation was reduced to 0 4 msec Six months after implant the infected leads were removed by thoracotomy At thoracotomy both were situated in an infected mass separated from myocardium The patient has remained pacing and sensing well the thoracotomy healed promptly In this case a variable output pulse generator was used to measure threshold changes and set output first to a safe and later to an energy-conserving level Even with successful transvenous electrode placement threshold rose briefly above the output of a conventional pacemaker The ability to increase output to override a temporary increase in threshold and to follow the evolution of that threshold was invaluable

Conclusions

The variety of analyses listed should indicate the possibility of careful analysis and resolution of problems of pacing More important an analysis of a pacing problem should include a variety of data not frequently obtained but readily ascertained and useful during clinical management



Fig 9 Intermittent pacing caused by inadequate placement of the electrode connector in the pul e generator receptacle *Left* the electrode pin is not adequately in the receptacle *Right* adequately placed the pin is deeper in the receptacle

Table I Factors responsible for malfunction of the lead system and their resolution

	Insulation					
	Fracture	*Failure*	*Displacement*	*High threshold*	*Poor sensing*	*Poor position*
Voltage	High	Low	High	High	Normal	High
Current	Variable May be normal	High	High	High	Normal	High
Impedance	High	Low	Normal	Normal	Normal	Normal
Electrogram	Variable	Variable	Low	May be normal	Low	Low
Resolution	Repair	Repair	Reposition	Higher output generator or reposition	High sensitivity generator	Reposition

four unsuccessful previous attempts at pacemaker implant a transvenous implant a revision of that implant a transthoracic implant and with its failure a second transthoracic implant With intermittent pacing he was referred to Montefiore Hospital and Medical Center X ray showed four myocardial electrodes two abandoned Medtronic 6913 and two Medtronic 6917 attached to a bipolar Medtronic 5950 pulse generator (Fig 10) At exploration the electrodes were detached from the pul e generator and all four were individually tested The two active 6917 electrodes had 1 msec stimulation thresholds of 5 7 mA (useful) and 12 3 mA (not u eful) The unipolar impedance for each was 400 ohms The two abandoned 6913 electrodes had thresholds of 14 0 milliamperes for one and 3 5 milliamperes for the other Clearly two of the four electrodes had a stable chronic and useful threshold though one was better than the other A Cordis 162D pulse generator allowing non invasive threshold measurement was attached Pacing has been consistent No unpaced cardiac activity exists This patient had two chronic stable electrodes out of the four implanted He required determination of which they were which was superior and then he needed conversion to unipolar pacing Of the bipolar assembly with which he was first seen the negative output of the generator had been connected to the high threshold lead Had the reverse been the case satisfactory pacing would have existed

Case 5 Patient E R with complete heart block had been implanted with two Medtronic 6917 electrodes on the diaphragmatic surface of the right ventricle 31 months previously One electrode had been abandoned the other was attached to a Medtronic 5843 pul e generator He had had diaphragmatic stimulation with each pacer impulse for 31 months was uncomplaining and was seen only becau e of impending pacer battery exhaustion

At surgery both electrodes were evaluated Pacing through both leads as a bipolar assembly exhibited a thre hold at 1 msec of 3 8 milliampere with diaphragmatic stimulation present at threshold as it was with the active electrode a a unipolar which also had a threshold of 3 8 milliamperes The previously abandoned lead had a stimulation threshold of 4 0 milliamperes without diaphragmatic stimulation A new pulse generator Coratomic C 100 was attached to the previously inactive lead Pacing and sensing have been satisfactory and diaphragmatic twitch absent In this instance bipolar pacing or unipolar pacing through one of the two leads produced diaphragmatic stimulation The second lead was satisfactory

Case 6 Patient T L with complete heart block had undergone two previous transvenous implants with electrode displacement Subxiphoid implant of two Medtronic 6917 electrodes with a Medtronic 5950 pulse generator unto the diaphragmatic cardiac surface had al o failed Stimulation threshold was above 10 milliamperes at 1 msec for both electrodes the impedance was 400 ohms through each electrode so that the electrodes were structurally intact

Coratomic Inc Indiana Pa

Annotations

Brady Memo

Decisive diagnosis of bradyarrhythmias is not always simply made particularly in patients who develop it infrequently and transiently In many cases the conventional electrocardiograms always reveal only sinus rhythm in spite of repetitive recordings. His bundle electrogram is widely used and it may aid in making a diagnosis if definite abnormal findings can be obtained If it reveals negative data however existence of a high grade A V conduction disturbance can not be ruled out Because severity of the atrioventricular conduction disturbance may vary at different times and because His bundle recording is usually limited to one time for each patient detection of the precise moment of infrequent high grade bradyarrhythmias is of prime importance in making a complete diagnosis Several methods of precision have been used for this purpose For example electromagnetic recording with the long term electrocardiogram such as Holter scan run system or continuous monitoring of the electrocardiogram at the Coronary Care Unit Both methods have merits and demerits As for demerits the former is fairly expensive and the latter requires one whole room of the emergency facilities Recently we have devised a simple less expensive small unit for detection of infrequent and transient bradyarrhythmia in an asymptomatic or even in an unconscious patient

This equipment is composed of two main units an electronic memorizing system and trigger system (Fig 1) Each unit is 132 × 63 × 23 mm in size and weighs 215 Gm The electronic memorizing system was originally designed to memorize the electrocardiogram by asking the patient to push a button when he noticed abnormal sensations. Yet we can not use only this system to detect infrequent and transient bradyarrhythmia for in most cases of infrequent and transient bradyarrhythmia the patient does not feel any abnormality if the attack is insignificant or else the patient becomes unconscious if it is serious In either case the patient is unable to push the button and detection of arrhythmias is not made In order to make this memorizing unit start whenever bradyarrhythmia develops we devised the trigger system

Heart Memo EM 10 Fukuda Denshi Co Ltd Tokyo Japan

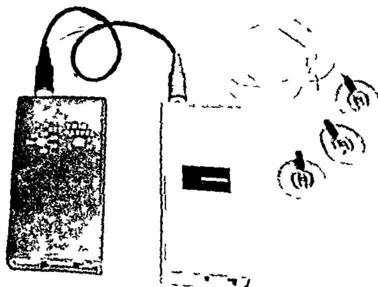


Fig 1 The Brady Memo the electronic memorizing unit (*right*) and trigger system (*left*) See text for operation

Such data as listed, voltage and current thresholds impedance and a measurement of the amplitude and slew rate or frequency of the cardiac electrogram, will be valuable to point out the resolution of the problematic case

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Durban However hypertension is not uncommonly asso ciated with cerebral atheroma and atheroma in the aorta

One of the striking features at autopsy among hypertensive patients is the rarity of myocardial infarction and the frequent occurrence of congestive cardiac failure and cerebrovascular accident as a result of hypertension A 10 year postmortem study (1965 to 19 4) among 434 African patients suffering from hypertension at King Edward VIII Ho pital showed that 41 9 per cent had cerebrovascular complication 25 per cent had renal complications, 32 9 per cent had cardiovascular complications in the form of congestive cardiac failure while only 10 patients (2 2 per cent) had myocardial infarction The average a e of the patients suffering from hypertension at autopsy was 45 years (range to 89 years) while the average age of the hyperten ive patients with myocardial infarction was 54 years Intracranial hemorrhage was responsible for 212 of the 23 cases (95 per cent) sufferin from cerebrovascular accident and cerebral thrombosis constituted only 11 cases (5 *per cent)*

At the Mama Yemo Hospital in Kinshasa Zaire one of us (H M F) studied the outpatient department of the Depart ment of Medicine In 19 2 344 386 patient consulted th outpatient department and of this total 8 603 (2 5 per cent) were cardiac in etiology Out of the 1 193 new patients 413 (35 per cent) were hypertensive There were no cases of myocar dial infarction in this study Available data in a significant number of admitted patients both normoten ive and hyper tensi e re eal that in most cases the serum cholesterol and uric acid le els were within normal limits

Seftel and associates from the Non European Hospital, Johannesbur recorded 4 African patients with myocardial infarction who were admitted to a medical unit of 40 beds over a 4 year period (1965 to 1968) Evidence was presented that the d ease is on the increase among the Africans in Johannes burg and this was a consequence of Westernization The two factors which differentiated the coronary sufferers most markedly from the general African population were a Western type of diet and a relatively sedentary existence Hyperten ion was present in 1 of the patients (50 per cent)

Other studies in Africans have hown that over a 10 year period (1961 to 19 0) in the University College Hospital, Ibadan 96 patients who suffered from myocardial infarction were seen The incid nce of the disea e in the ho pital population was 1 in 0 000 *The rarity of coronary atheroscle rosis* was thought to be related to environmental *rather than* to racially determined factors In 412 middle aged and elderly persons living at Kasangati (Uganda) hyperten ion was the dominant cardiovascular disorder occurring in 33 *per cent of* the study population A history of angina was elicited in a significant proportion of individual with obscure cardiomeg aly when *compared with* a control group Myocardial infarc tion was, however rare

The rarity of myocardial infarction in the Afri an i in contrast to the work of Breckenrid e *and colleagues* who found that in the period 1960 to 196 among 03 patients that myocardial infarcti n occurred in 2 per cent of the hypert n si e patients at Hammersmith Hospital London Smirk *and* Hodge *in* New Zealand in a series of 8 hyperten ive patients who died between 19 9 to 1961 found that coronary artery disease accounted *for 41 5 per cent* of all deaths and was the most common ingle cause of death In the American Negro in a 100 unselected patients, per cent had evidence of arterio-sclerotic heart disease and 81.8 per cent had either diastolic or systolic hypertension

The Framin ham Study found that increased lipid hyper tension cigarette smoking overweight and diabetes mellitus were predisposing factors for myocardial infarction The urban African has all the above predi posing factors with the exception of increased serum lipid Walker found that in the 30 to 39 year age group a serum cholesterol above 220 mg per 100 ml was present in 55 per cent of Whites 45 per cent of Indians 25 per cent of urban Africans and 10 per cent of rural Afri ans in South Africa The proportions of Whites with a raised serum cholesterol was much the same as reported in the Framingham Study—namely 58 per cent Trowell and asso ciates proposed that a fiber deficiency may help to cause not only diverticulo is but also i chemic heart disease Thus it is possible that the high dietary fiber of the African may protect him not only from diverticulosis but also from ischemic heart disease Trowell and colleagues state that historically and epidemiologically diverticulitis and ischemic heart disease are closely associated and the few experiments that have been carried out also support the view that dietary fiber can affect serum cholesterol levels

The studies in Africa suggest that hypertension is not an important predi posing factor in the etiology of myocardial *infarction However it may be an important correlate with* other factors that predi pose to myocardial infarction rather than a causal factor Akinkugbe has aptly *stated "It seems* remarkable therefore that hypertensive Africans seem readily to go into heart failure in the absence of coronary artery *disease*

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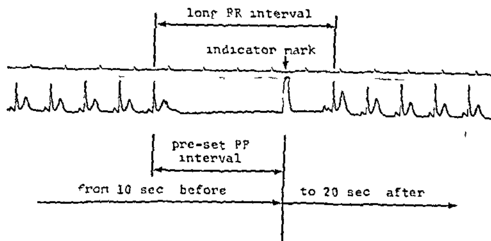


Fig 2 Typical ECG memorized by the Brady Memo device See text for details

This trigger system is a detecting device discriminates R waves of the patient s electrocardiogram If the RR interval of the patient becomes longer than the pre set RR interval this trigger system is effective and the electronic memorizing unit memorizes the electrocardiogram at the event One can adjust the pre set RR interval as desired by moving a dial on the trigger unit

Once the units memorize the event one can reproduce the electrocardiogram by connecting the unit to the DC input of a conventional electrocardiograph Fig 2 illustrates an example of electrocardiogram memorized by the Brady Memo which was tested by using a simulated electrocardiogram The interval from the preceding QRS complex to the indicator mark represents the pre set RR interval The actual RR interval at the event is longer than the pre set RR interval The electronic memorizing system can memorize the electro cardiogram for a full thirty seconds from ten seconds before to twenty seconds after the indicator mark

This less expensive simple Brady Memo detects transient asymptomatic bradyarrhythmia whenever the RR interval becomes longer than the pre set interval It will be of great help in detecting infrequent and transient bradyarrhythmia and greatly contribute to diagnosing and managing a patient with latent or suspected high grade bradyarrhythmia

At present we conclude that combination use of His bundle electrography and other supplemental methods which can detect transient or infrequent high grade A V block is the best way to manage these patients

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Since the submission of this article we have invented a new model Two Steps Brady Memo This new model has two sets of memory systems and a trigger system with two different pre set intervals i e a relatively short pre set interval of 2 0 seconds or less and a long pre set interval of 5 0 seconds or more This can detect more easily transient bradyarrhythmias with different grades in one setting

Myocardial infarction in the African hypertensive patient

Hypertension is common in the urban African Yet myocardial infarction is rare even though there is a high incidence of congestive heart failure as a result of hypertension In the urban African in Johannesburg hypertension and its complications is believed to be the second most common cause of death in the adult after violence

One of us (Y K S) has studied 1 000 hypertensive patients (500 Africans and 500 Indians) who were followed for over a period of 13 years The incidence of cardiac changes revealed that while congestive cardiac failure due to hypertension occurred in 16 per cent of the Africans ischemic heart disease did not occur This is in contrast to the Indian population in whom myocardial infarction or angina occurred in 12 per cent of cases King Edward VIII Hospital Durban has 2 000 beds and serves a population of 2 million there are approximately 880 000 patients attending the outpatient department and about 100 000 are admitted to the hospital per year (Africans 83 per cent Indians 17 per cent) While myocardial infarction is common in the Indian the number of cases of myocardial infarction or angina in Africans does not exceed 10 per year The incidence of coronary atheroma in Africans at necropsy is far less than in the European or Indian population in

ECG changes were concomitant to anginal pain in nine of 12 cases (4) such reversal of previously negative T waves is known to occur during exercise indu ed is hemia in patients with chronic coronary insufficiency

During the course of ischemic heart disease episodes of acute myocardial ischemia may result in misleading modifica tions of the ECG such as a transient appearance of abnormal Q waves (ischemic Q waves) Isolated (that is without ST segment changes) reversal of negative T waves which become upright is another unusual electrocardiographic aspect of the ischemic process it may result at times in a transient normalization of the repolarization The fact deserves to be known as the spontaneous ECG changes may occur silent ly without anginal pain (three of 12 cases) and are not to be interpreted as an improvement of the patient s status On the contrary they may herald serious incidents (myocardial infarction and/or severe ventricular arrhythmias in three of our cases) and may necessitate a close watching of these patients

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Of central venous pressure

A pressure recording from the ri ht atrium or superior vena cava or from any place records levels of pressure and not volume The central venous pressure reflects the ten ion of the wall of the right atrium or vena cava In no way does this ten ion alone reflect blood volume Whether or not a patient is hypovolemic or hypervolemic mu t be determined from mea urements of blood volume or phy iologic data which reflect volume of blood For example central venous pres ure is elevated in right ventricular congestive heart failure but blood volume may or may not be increased As indicated previously the pres ure in a blood vessel or a chamber of th heart is dependent upon the tone or ten ion of the wall of the vessel or chamber u ua ly due to the state of contraction of the mu le of the wall To accept non-critically the level of central venous pressure as a quantitative index of blood volume can only lead to phy iologic and/or therapeutic errors Central venous pres ure recording is a recording of pressure only

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Pseudo normalization of the repolarization during transient episodes of myocardial ischemia

Myocardial ischemia is known to alter the repolarization resulting mainly in T wave changes and/or ST segment displacement normal T waves become negative (subepicardial ischemia) or tall and peaked (subendocardial ischemia)

We would like to draw attention to an electrocardiographic sign which deserves to be known as it may be misinterpreted whenever the basal electrocardiogram (ECG) is abnormal presenting with negative T waves the occurrence of a new ischemic episode may result in an isolated (without ST changes) reversal of T waves with at time subsequent *pseudo normalization of the repolarization*

We recently observed 12 such cases there were five males and seven females age ranged from 53 to 80 years (average 65 0 years) *In all cases negative T waves became suddenly upright for a short period of time (a few hours to 3 days) and* then the tracing reverted to the previous status (Fig 1) in all *cases the transient T wave changes occurred during the* hospitalization course of an acute coronary process (recent myocardial infarction—10 acute coronary insufficiency—2) they were more frequently present in precordial lead (11 of 12 cases) than in postero diaphragmatic leads (1 of 12 cases) Anginal pain was present in nine of 12 cases it occurred simultaneously with ECG changes in seven cases and followed ECG changes in two cases in three cases the T wave reversal was silent Serum enzyme (SGOT SGPT LDH HBDH CPK) levels did not increase during the three days following the transient inversion of T waves Complications occurred in three cases within two weeks after the ECG changes (ventricular *fibrillation—1 myocardial infarction—2)*

In our study reversal of previously negative T waves resulted most likely from a new ischemic episode since (1) *there was no evidence of other causes of transient modification of the repolarization and mainly no signs of pericardial* effusion hypo or hyperkaliemia (2) ECG changes were transient and subsided within one day in eight of 12 cases (3)

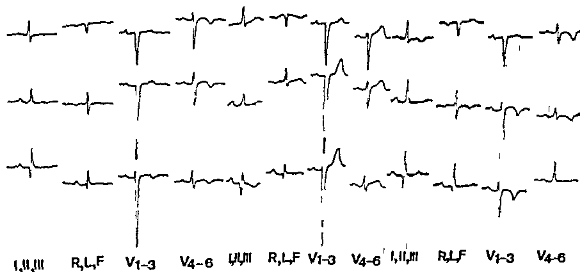


Fig 1 Case 3 *Left* on the basal ECG patterns of an old postero diaphragmatic and a recent anteroseptal MI are present T waves are negative from Leads V to V *Middle* during an anginal pain T waves become upright in the precordial leads *Right* one day later the tracing has reverted back to the previous state and T waves are again negative in the precordial leads

ECG changes were concomitant to anginal pain in nine of 12 cases (4) such reversal of previously negative T waves is known to occur during exercise induced ischemia in patients with chronic coronary insufficiency

During the course of ischemic heart disease episodes of acute myocardial ischemia may result in misleading modifications of the ECG such as a transient appearance of abnormal Q waves (ischemic Q waves) → Isolated (that is without ST segment changes) reversal of negative T waves which become upright is another unusual electrocardiographic aspect of the ischemic process it may result at times in a transient normalization of the repolarization The fact deserves to be known as the spontaneous ECG changes may occur silently without anginal pain (three of 12 cases) and are not to be interpreted as an improvement of the patient s status On the contrary they may herald serious incidents (myocardial infarction and/or severe ventricular arrhythmias in three of our cases) and may necessitate a close watching of these patients.

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Of central venous pressure

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Central venous pressure recording is a recording of pressure only

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Letters to the Editor

Coronary thrombosis and acute myocardial infarction cause or consequence?

To the Editor

Classical pathologic findings established a cause effect relationship between coronary thrombosis and acute myocardial infarction This simple and logical concept is now challenged after more than twenty years

In a recent paper which appeared in the AMERICAN HEART JOURNAL Baroldi finds an arterial occlusive thrombosis in only 38 per cent of acute myocardial infarctions with an increase directly related to the increase of the infarct size and the survival time

I believe myocardial infarction is to be rigidly defined as emphasized by Davies and co workers a localized area of muscle necrosis in the myocardium visible to the naked eye at necropsy and larger than 3 cm in diameter in an axis

I reviewed my last 60 postmortem examinations (all performed by myself) of patients who died from a first acute transmural myocardial infarction within the first month following the onset of the symptoms In all the cases the diagnosis of acute myocardial infarction was previous to death sustained by usual clinical features (chest pain of long duration) and/or electrocardiographic and biological patterns

The 60 necropsy studies include 32 myocardial infarcts involving the anterior wall of the left ventricle 25 involving the postero inferior wall and three involving the lateral wall In all the cases but four (93 33 per cent) I have found an occlusive coronary thrombosis located in a major artery which subtended the infarct In all these 56 cases the thrombus was located in a narrowed segment (from 45 to 95 percent) of a major coronary artery at the level of an atherosclerotic ruptured plaque These findings are totally in agreement with those of Chapman and of Davies and co workers

There was no relation between sex age location of the infarct and the presence (56 cases) or the absence (four cases) of an occlusive coronary thrombosis

In the four cases where no thrombosis was found (three anterior one inferior infarcts) the lumen of the coronary artery which subtended the necrotic area was narrowed more than 90 per cent (death occurring on the first third fourth and 28th days)

In 48 cases the coronary artery below the thrombosis was most of the time atherosclerotic and narrowed but the distal border of the thrombus was separated at least by 15 mm from the upper part of the destroyed muscle In eight cases the thrombus was very close to the infarct but in all these eight cases the muscular mass involved by the located ischemic necrosis (six anterior two postero inferior infarcts) was always equal or larger than 35 per cent of the total mass of the free walls of the left ventricle and interventricular septum (death occurring from the second to the 14th day)

I did not find any relationship between the size of the infarct and the occlusive arterial coronary thrombosis (size of the infarct less than 20 per cent seven cases six thromboses 30 to 39 per cent 17 20 to 29 per cent 13 cases 13 thromboses 30 to 39 per cent 17 cases 14 thromboses 40 to 49 per cent 14 cases 14 thromboses 50 per cent and more nine cases nine thromboses $P > 0.05$) Neither did I find a relationship between coronary thrombosis versus survival time death before the third day 17 cases 16 thromboses from the third day to the tenth day 25 cases 23 thromboses from the 11th to the 30th day 18 cases 17 thromboses $p > 0.05$) At least in agreement with Chapman I have never found coronary thromboses in the veins associated with myocardial infarction

These purely anatomic facts are nearly the same as those exhibited by Chapman and by Davies and co workers They may become more acceptable since as emphasized by Chapman and by Davies and co workers there is a nearly constant and probably causal link between occlusive coronary thrombosis primary event and acute myocardial infarction This opinion seems to be the conclusion of the recent report of the workshop on the role of arterial coronary thrombosis in the pathogenesis of myocardial infarction

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Reply

To the Editor

I would like to thank the Editor of the AMERICAN HEART JOURNAL for giving me the opportunity to reply to both the letter of Dr Penther and indirectly to the quoted paper of Dr Davies and associates which states It is hardly credible that there should be continuing debate about what is ostensibly so simple a morphologic problem—the relation of coronary thrombosis to acute myocardial infarction For centuries it was also ostensibly simple that the earth was the center of the universe and those who postulated otherwise were similarly dismissed as radicals and heretics of the time

Most of the debate here concerns the frequency of the thrombus while I believe that what is essential is to discuss the effectiveness of the thrombus in reducing or stopping blood flow in the dependent coronary artery To look only at the frequency of the thrombus is to look only at the sun seemingly running its course from east to west without consideration for the behavior and interaction of this body in context to the whole universe Metaphors aside we need to know not only where the thrombus is located but all of the

intervening factors as well Despite the findings of Dr Penther (apparently he demonstrated acute thrombus in vessels with a lumen reduction of 45 per cent—did he check by 3 mm transverse sections all the vessels in his reviewed" material?) I found in all my cases thrombus in ves els already severely tenosed by chronic atherosclerotic change Furthermore in all cases of acute myocardial infarction with severe old obstructive coronary damage it was possible to demon trate a well-developed collateral system equal to that found in cases with the same coronary damage without infarction Based on these findings I proposed—and confirmed experimental ly —that the thrombus when found, may have little if any ischemic significance Therefore even if we can demonstrate a thrombus located in a vessel with severe stenosis in all cases of myocardial infarction this does not necessarily imply that the thrombu is the cause of the infarct The contrary may be true as suggested by cases with secondary occlusion of a bypassed stenosis the bypass being hemodynamically peak ing the equivalent of the collaterals I need not reemphasize that some criticisms on the collateral function are inconsis tent My first conclusion therefore is that to limit the discussion to the frequency of the thrombus is just to scrape the surfa e

Dr Penther states that I found an increase in frequency of thrombi "related to infarct size and the survi al time Dr Penther needs to read my editorial again and perhaps some other papers of mine On page 685 it clearly states that no correlation was found with the survival time We agree on at least one point On the other hand we have opposite data on the relation of infarct size to the frequency of the thrombus Dr Penther peaks of percentage and I would like to know how he measured that I am just a little surprised that even in his cases with less than 20 per cent infarct size all showed an occlusive thrombus since he defined an infarct size according to the criteria of Davies and associates as localized area of muscle in the myocardium visible to the naked eye at microscopy and larger than 3 cm in diameter in one axis" Thus a 20 per cent infarct with a 3 cm major diameter is frequently an internal more or less laminar lesion a condition in which m ny authors found a low frequency of thrombus including Dr Sinapius a sustainer of the classic view who participated in the quoted workshop and who found a 55 per cent frequency of thrombus in infarcts of less than 4 cm in diameter I understand that a letter is only a letter but when one is trying to present criticism it should be presented in a paper defining the methods employed much as Dr Da ies and associates have done So that it is poss ble to know if they measured the percentage of the infarct size the degree and length of the stenosis and the other variants that we checked Furthermore their rigid criteria by which the material is selected is questionable Only coroner s cases i e sudden death cases, w re excluded I wonder how many surgical cases were included Further to define an infarct as only a 3 cm or more l sion" is a very unu ual means of classification What do we mean that a pathologic entity has to be defined according to the size of the lesion? In selecting our cases we chose only those in which there was (a) a typical clinical pattern without other cardiac and noncardiac disease and with ut surgical intervention and (b) histologic evidence of coagulation necrosis with polymorphonuclear infiltration of its sequelae regardless of size In my opinion these are more rigid criteria that help in understanding the natural history of coronary h art disease keeping in mind that one must not confuse the different types of myocardial necroses frequently associated with this disease In my editorial I question the significance of the distinction between small and large infarcts Dr Davies and associates state "It is to be regretted that diffuse circumferential subendocardial necrosis is still classified by many observers (referring to Baroldi and col leagues 19 4 and Ehrich and Sinohara 1964) as myocardial infarction To this limited list of observers one has to add those pathologists who participated in the referenced work shop since they all spoke of a "small infarct as a patchy multifocal often subendocardial lesion rarely associated with an occlusive thrombus likely due to coronary insufficiency The problem is not one of semantics since people die with the same signs and symptoms and the same histologic lesion regardless of its size What we need to determine is why they die in other words, the patho enesis of the disease The controversy will continue until we are able to study and assess all the variants of the phenomenon and not just the frequency of the thrombus in the reviewed" material.

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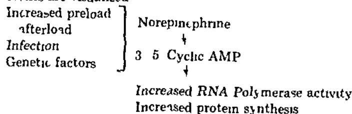
Catecholamine induced hypertrophy

To the Editor

In a recent annotation Laks and Morady ug ested that norepinephrine may be the ultimate myocardial hypertrophy hormone We wish to support this hypothesis It is well known that other sympathomimetic agents such as isoproterenol and amphetamine also prod ice cardiac hypertrophy In our laboratory we are regularly able to produce 45 per cent cardiac hypertrophy in five days with i oproterenol in a daily dose of 10 mg /Kg

In the cardiomyopathy of the Syrian Golden hamster we have found increased myocardial adenyl cyclase activity All

of these facts suggest that either an increase in preload or afterload or some genetic process or for that matter an infectious agent such as a virus results in the release of norepinephrine in the myocardium The following chain of events are visualized



Eventually as Meerson[5] has suggested with chronic overload a decrease in the compensatory response leads to congestive heart failure

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Norepinephrine—the producer of myocardial cellular hypertrophy and/or necrosis and/or fibrosis

To the Editor

We agree with Dr Nair's and Dr Dhurjaty's placing norepinephrine in a central mechanistic position responsible for the production of ventricular cellular myocardial hypertrophy However *we question the singular conclusion of Dr* Meerson—a chronic overload to the ventricles results in myocardial hypertrophy and finally leads to congestive heart failure We consider *that these conclusions have unfortunately* evolved from the wrong type of animal models utilized for the production of myocardial hypertrophy in that they do not simulate the clinical entity *that results in myocardial* hypertrophy and congestive heart failure specifically most of these methods utilized required the production of an acute and severe obstruction to the right or *left ventricle This fact* was the motivating influence for us to establish a method for production of an afterload to the right ventricle in which the afterload could be varied and produced in a *conscious dog In* contrast to the observations and conclusions of Dr Meerson *we have demonstrated that* mild to moderate afterload to the left ventricle for a period of one year did not result in congestive heart failure and myocardial fibrosis but rather produced an increase in myosin ATPase in the right ventricle and a normal ATPase in the left ventricle This observation is in concert with the studies of Wikman Coffelt and colleagues who had demonstrated that mild banding of the pulmonary *artery resulted in an increase in right* ventricular myosin ATPase activity We indeed agree that catecholamines can produce a myocardiopathy which consists of myocardial necrosis and/or fibrosis and/or myocardial cellular hypertrophy *We reported a case of a patient taking an overdose of the* catecholamine isoproterenol which resulted in electrocardiographic and cardiac serum enzymatic changes consistent *with myocardial necrosis Therefore we agree that* catecholamines can indeed be destructive to the myocardium However we consider that the problem of catecholamines and its good and evil effects are probably analogous to the problem in the models for the production of myocardial hypertrophy in that a low progressively increasing dose of norepinephrine can produce hypertrophy of the myocardium without necrosis and a myocardium which has an increase in its ventricular function This concept evolves from our studies in which we reported that an increase in ejection fraction was produced by a subhypertensive infusion of norepinephrine in conscious dogs over a period of 4 to 7 months

In summary in contrast to the view of Dr Meerson we consider that in a better functioning hypertrophied heart *so called physiological hypertrophy can be produced by* a mild progressive increase in the overload to the ventricle and by a low progressively increasing dose of norepinephrine In addition *we indeed agree that norepinephrine plays a central role* in the process for the production of myocardial cellular hypertrophy

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Book reviews

Cardiac Pacing Diagnostic and Therapeutic Tools Edited by B Luderitz New York 1976 Springer Verlag 245 pages

The papers presented at a symposium held during November 1975 in Munich are bound in this book edited by Luderitz The material discussed was concerned with (1) sinus node (2) atrioventricular conduction and (3) supraventricular and ventricular tachycardias The several presentations related to each of these general subjects review very well the present approach in diagnosis and management The presentations are brief and well illustrated but as is the tendency these days, the literature is poorly reviewed and well established concepts and studies ignored and not well integrated with present considerations and practices There has really been very little new developments in these fields as is evident from considerations of publications of studies and practice of a few decades past The use of pacing for complete heart block has been of clinical importance and value in patient care The theoretic considerations and application of investigations of the three above listed subjects are well described however This is an important publication not only because of the frequency of serious cardiac arrhythmias and the use of pacemakers but because of the need to learn how to prevent the occurrence of these arrhythmias This is a valuable addition to cardiology

The Heart and Circulation Edited by Peter A Chevalier New York 1976 Halsted Press 386 pages Price $26 00

This is the eighth publication of the *Benchmark Papers in Human Physiology* Chevalier divided his book into four parts i.e (1) cardiac output–control and adaption (2) coronary flow and cardiac metabolism (3) the conduction system of the heart–anatomic description and (4) the systemic circulation–peripheral vascular control The editor has selected several papers from the literature which he considers important He probably had a great deal of difficulty deciding what to include and what to exclude among his selections This reviewer can think of from the historical point of view other publications which were the basis for physiology states now taken for granted in physiology To name one–the work of Huxley on the ultrastructure of striated muscle Another the classic studies of Thomas Lewis are extremely important contributions to the understanding of the circulation in man Regardless of differences of opinion this book does have in one binding interesting and important papers published in the past Physiologists in particular will find the papers in this book worth reviewing

Coronary Heart Disease Clinical Angiographic and Pathologic Profiles By Zeev Vlodaver M D Kurt Amplatz, M D Howard B Burchell M D., and Jesse E Edwards M D New York 1976 Springer Verlag 584 pages $6 50

This is an excellent publication of 1,202 illustrations, accompanying brief text and legends of selected aspects of coronary heart disease The authors are highly experienced in cardiology with special interest in clinical medicine The 16 chapters are concerned with anatomy of the coronary vessels coronary angiography with disease of the coronary vessels anomalies of the coronary arteries pathologic and physiologic correlations with coronary angiography angina pectoris infarction and surgical care The illustrations are very clear and well selected and the associated diagrams presented as inserts are extremely helpful in interpretation of the photographs. This is a highly recommended book for all who are interested in heart disease

Advances in Cardiology Physical Activity and Coronary Heart Disease Edited by Vesa Manninen and Pentti I Halonen New York 1976 S Karger AG 270 pages. $50 00

This volume should interest all cardiologists and especially those who strongly advise their patients to exercise Many physiologic and biochemical aspects of the changes produced by exercise are considered For example the influence of exercise on heart size and mass cardiac rhythm cyclic AMP collagen metabolism coronary blood flow and myocardial use of O clinical state of the heart coronary atherosclerosis hormones, lipid metabolism platelets risk for myocardial infarction and longevity These are all important considerations among many more As with any symposium attendance is better but for the many interested people who did not attend, this book presents very well and clearly the discussions which developed at the meetings in Helsinki.

Announcements

National Conference on Clinical Trials Methodology

The National Conference on Clinical Trials Methodology will be held in Masur Auditorium NIH Bethesda Md on October 3 and 4 1977 Topics will focus on the importance of clinical trials their termination investigators and incentives patient recruitment quality assurance ethical problems and improving communication Lecturers will include Drs Donald S Fredrickson Curtis Meinert Robert Gordon Thaddeus Prout O Dale Williams Robert Levine Harold P Roth and Mr Fred Ederer No registration nor notification of planned attendance is required

For additional information please contact Dr Robert Gordon Bldg 1 Room 107 National Institutes of Health Bethesda Md 20014

Pediatric and Adolescent Echocardiography course

The third annual Pediatric and Adolescent Echocardiography course 1977 will be presented Nov 25 through 27 (the weekend preceding the American Heart Association meetings) in Miami Beach Florida The course is sponsored by the American Society of Echocardiography the American Institute of Ultrasound in Medicine and the Postgraduate Educational Division of H E L P and is approved for Category I Continuing Medical Education Credit by the American Medical Association Faculty includes Drs Stanley J Goldberg Hugh D Allen David J Sahn Walter Henry Richard Meyer and Arthur Weyman

Further information may be obtained from Pediatric Echocardiography Course 4340 Placita Panuco Tucson Arizona 85718 (telephone 602/887 6508)

Third International Joint Stroke Conference

The third International Conference on Cerebrovascular Disease and Cerebral Circulation will be held at the Fairmont Hotel in New Orleans La on February 16 through 18 1978 Sponsored by the Stroke Council of the American Heart Association the meeting is held in conjunction with the Cerebrovascular Surgery Section American Association of Neurological Surgeons the Canadian Stroke Society the Canadian Heart Association and the Society for Vascular Surgery Robert C Siekert M D of the Mayo Clinic is serving as the Conference Chairman

Guidelines and further information may be obtained by writing Administrator Postgraduate Programs American Heart Association 3 0 Greenville Ave Dallas Texas 7 31

Einthoven Symposium on Developments in Electrocardiography

In commemoration of Willem Einthoven's death 50 years ago the Einthoven Symposium on Developments in Electrocardiography 1977 19 will be held in the lecture hall of the Laboratory of Physiology Wassenaarseweg 6 Leiden The Netherlands on Friday October 28 1977 For further information regarding this symposium please contact A C Arntzenius, Department of Cardiology University Hospital Leiden Rijnsburgerweg 10 Leiden The Netherland

Prize for paper on Preventive Medicine

A $500 cash prize will be awarded by the American Health Foundation's quarterly journal *Preventive Medicine* to the student author of the best original paper on the subject of preventive medicine A runner up prize of $200 is also being awarded Winning papers will be published in the Journal

The contest is open to any student (*except* postdoctoral students) currently enrolled in undergraduate or graduate courses in medicine dentistry public health pharmacy nursing life sciences, nutrition the social and behavioral sciences, economics, law or business

For entry forms and information please write to The Editorial Office Preventive Medicine American Health Foundation 1370 Avenue of the Americas, New York N Y 10019

International Congress on Hypertension

An International Congress on Hypertension sponsored by the Cardiological Society of India Bombay Branch will be held on October 7 through 9 1977 in Bombay India For further information regarding the congress write to Dr N J Shah Bombay Hospital Trust Bombay 400 020 India

International Cardiopulmonary Symposium

An International Cardiopulmonary Symposium will be held at the Hotel President in Bombay India on November 13 through 15 1977 The symposium is being sponsored by the Western India Chapter of the International Academy of Chest Physicians and Surgeons (affiliated with the American College of Chest Physicians) by the Association of Physicians of India and its Bombay branch and by the Indian Association for Chest Diseases. Many international authorities will participate in the symposium which will deal with advances in cardiopulmonary medicine and surgery

For further information regarding the symposium write Dr M Paul Anand Secretary General International Cardio Pulmonary Symposium 4 Narendra Bhuvan Bhulabhai Desai Road Bombay 400 026 India

Cardiovascular Stress Testing Seminar

A Cardiovascular Stress Testing Seminar will be held on November 3 through 6 1977 at the Convention Center Little Rock Arkansas. The seminar is sponsored by the Division of Cardiology University of Arkansas for Medical Sciences Early preregistration is required since enrollment is limited This Continuing Medical Education offering meets the

Books received

Exercise Testing of Cardiac Patients By M Kaltenbach Prof Dr Med Berne Switzerland 1977 Hans Huber Verlag 126 pages Price 26 Swiss francs

High Resolution Electrocardiography A Superior Diagnostic Modality By Lawrence H Krohn M D M S Springfield Ill Charles C Thomas Publisher 264 pages Price $28 50

Progress in Cardiology 5 By Paul N Yu M D and John F Goodwin M D Philadelphia 1976 Lea & Febiger Publishers 365 pages Price $19 50

Bulletin of the World Health Organization Atherosclerosis of the Aorta and Coronary Arteries in Five Towns World Health Organization Health & Biomedical Information Programme 1976 Geneva Switzerland 160 pages Price $7 20

International Symposium on Preventive Cardiology The Irish Heart Foundation Dublin Ireland 1976 174 pages

Pleural Effusions A Comprehensive Review By James R Lowell M D Baltimore 1977 University Park Press 143 pages Price $14 50

Medical Emergencies Diagnostic and Management Procedures from Boston City Hospital Edited by Alan S Cohen M D Ralph B Freidin M D and Martin A Samuels M D Boston 1977 Little Brown & Company 260 pages Price $15 00

Guide de Cardiologie du Sport By F Plas Paris 1976 Laboratoires Besins Iscovesco 147 pages

Anatomie des Arteres Coronaires du Coeur By C Christides and C Cabrol Paris 1976 Laboratoires Besins Iscovesco 190 pages

American Heart Journal

October 1977 Vol 94 No 4

Editorial

Blood pressure in infancy

Michael de Swiet M D *
Elliott A Shinebourne M D
London England

Hypertension is a major risk factor in death from all vascular diseases There have been several epidemiological studies on the prevalence of hypertension in the adult population[2] However there are few studies on the prevalence and evolution of hypertension from the neonatal period There are also few accurate cross sectional studies of blood pressure in an adequate population of infants or young children[3,5]

One of the main reasons for this lack of data has been the practical difficulty of measuring blood pressure accurately by a non invasive technique in neonates and small children This difficulty has now largely been overcome by the Doppler ultrasound technique which detects blood flow by the Doppler shift produced by moving blood particles A sphygmomanometer cuff is placed around a limb inflated above systolic blood pressure and then deflated in the normal way The pressure at which blood flow is first detected by an ultrasound probe placed over an artery distal to the cuff is taken as the systolic blood pressure We have found that intra arterial blood pressure is closely correlated with blood pressure measured by doctors or nurses using the Parkes Doppler ultrasound system We have also evaluated the Roche Doppler Arteriosonde system[7] which is said to measure diastolic as well as systolic blood pressure in infants Indirect measurements were again compared with intra arterial measurements The correlation of Arteriosonde blood pressure and intra arterial systolic blood pressure was not so close as the correlation of Parkes and intra arterial blood pressure measurements The correlation of the Roche diastolic blood pressure measurements with intra arterial blood pressure measurements was poor (r = 0 51) We therefore do not believe that the Arteriosonde can measure diastolic blood pressure accurately in infants though the Infrasonde machine may well do so We have continued to use the Parkes instrument since we find it convenient Since systolic blood pressure is a better predictor of cardiovascular mortality in adults than is diastolic blood pressure[8] we are not concerned that we have been measuring systolic blood pressure only in our epidemiological studies

Since we wished to obtain a representative measurement of blood pressure in the neonatal period we first studied blood pressure variability in the first six days of life We found that blood pressure increased most rapidly during the first four days of life and thereafter it became more stable We therefore chose to measure blood pressure in the infants of the population study at age 4 to 6 days when they were not crying or feeding activities which both raise blood pressure We and others[11] have found that blood pressure higher in babies awake than in babies who are asleep The difference was 11 mm Hg in our neonatal series Therefore in our epidemiolog

From The Cardiotho acic In t tut Brompton Hosp tal, Fulham Road, Lo d n Engla d

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Reprint requests Mi hael de Swi t M D D pt of Paed tri The Cardiothoracic Institute Brompt n Hospit l Fulham Road Lond n SW3 6HP E gla d

* M ch el d Swiet was suppo ted by G a t from The Med al Research C u cil

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criteria for 12 hours of credit in Category I for the Physicians's Recognition Award of the American Medical Association

For further information please contact Dr John E Douglas University of Arkansas For Medical Sciences 4301 West Markham Little Rock Ark 72201

Prevention and Reversal of Atherosclerosis Cruise symposium

A Prevention and Reversal of Atherosclerosis Cruise symposium will convene aboard the luxury cruise liner S S Emerald Seas sailing from Miami on January 30 1978 to Freeport and Nassau in the Caribbean and returning to Miami on February 3 1978 Program subjects include Clinical Intervention Trials New Antiatherosclerosis Drugs Technology of Regression Assessment Hyperalphalipoproteinemic and Hypobetalipoproteinemic Agents Phospholipids for Atherosclerosis Regression and other topics Ship accommodations run from $305 to $340 U S funds

For further information and forms please contact Dr Charles E Day Atherosclerosis Project Leader The Upjohn Company Kalamazoo Mich 49001

Advancement of Tension Control meeting

The fourth annual meeting of the American Association for the Advancement of Tension Control will be held in Chicago at the Bismarck Hotel on October 15 and 16 1977 For further information regarding this meeting please write F J McGuigan Ph D Executive Director A A A T C P O Box 7 ol? Roanoke Va 24019

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21 Department of Health and Social Security Present-day practice in infant feeding London 19 4 Her Majesty's Stationery Office
22 Oates R K Infant feeding practices, Br Med J 2 62 1973
23 de Swiet M Cooper L V and Fayers F Unpublished observations

ical study[12] we corrected blood pressure for level of consciousness

We have subsequently embarked on a population study of 2 000 infants in an attempt to identify a sub group who may develop hypertension We elected to study a relatively stable, well defined population—all infants born at Farnborough Hospital, Kent whose mothers live in the London Borough of Bromley Blood pressure is measured by a team of four nurses at home or in hospital at 4 days, and in the infants' homes at age 6 weeks, 6 months, 1, 2, and 3 years

Analysis of the data from the first 500 infants to enter the study[12] has enabled us to present cross sectional data on the normal blood pressure distribution at age 4 to 6 days and at 5 to 7 weeks of age The distributions are the same for boys and girls We have confirmed our previous finding[10] that wakefulness is associated with increased blood pressure at both 4 to 6 days, and at 5 to 7 weeks

We have also found a highly significant ($r < 0.001$) relationship between blood pressure at age 4 to 6 days and blood pressure at age 5 to 7 weeks[1] If the correlation holds in later measurements it would suggest that it may indeed be possible to identify at birth a sub group of children at risk from hypertension, particularly as it has already been shown that blood pressure in infants aged 2 to 14 years is correlated with blood pressure measured in the same infants four years later[11] The correlation that we observed was not strong ($r = 0.20$), but this is of the same order as had been noted in other studies such as Zinner, Levy and Kass s familial studies[14]

Hennekens and associates[15] found evidence of familial aggregation of blood pressure at age one month but not at age 2 days This was based on measurements of blood pressure made in the siblings of the index infant We have not made any measurements in siblings but we have found no correlation between mother s or father s blood pressure and infant s blood pressure at age 4 to 6 days or at age 5 to 7 weeks[1] Lee and co workers[11] also did not find a correlation between maternal and child systolic blood pressure in the neonatal period, although they did find a weak correlation in diastolic blood pressures We would expect to find a significant relationship as the children grow older and their blood pressure variability becomes less The mother s blood pressure could also have been affected by pregnancy even six weeks after delivery[16] and the mother's blood pressure variability will also be less once she is past the immediate postpartum period

Despite the evidence that sodium intake may be related to the development of hypertension,[17 19] we have been unable to find any relationship between blood pressure measured in infancy and sodium intake Miall[20] was unable to find a correlation between blood pressure measured in adult life and sodium intake We have examined this relationship in two ways

First the majority of infant feeding preparations used in the United Kingdom have about twice the sodium concentration of human milk[21] and this concentration may be increased still further if the feed is mixed incorrectly[22] But at ages 4 days and 6 weeks there was no difference between the blood pressures of bottle fed and breast fed babies[23]

Secondly blood pressure was not related to the sodium content of feeds in measurements taken at age 6 weeks in a group of babies who were being bottle fed alone[21] This relationship will be re examined as the children become older

At present we believe that we can identify a population of infants with a risk of developing hypertension but because correlations are weak though highly significant we cannot identify individual babies at risk Repeated measurements may reduce the variability as may measurements under more standard conditions such as exercise If this occurs we will then be obliged to consider whether we should intervene in the progress of these infants towards hypertension and if so how

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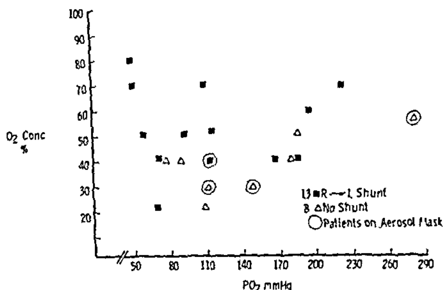


Fig 1 This figure illustrates the relationship between the inspired oxygen concentration (O_2 conc %) and the resultant arterial Po (Po mm Hg) in the 21 patients. □ = patients with right to-left intracardiac shunt. △ = patients with no intracardiac shunt. ○ = patients using an aerosol mask the inspired O concentration is thus an approximate value

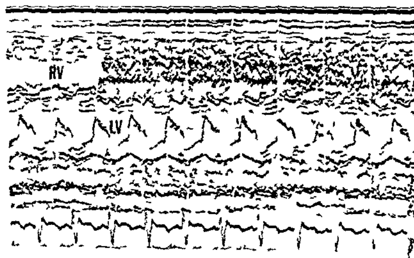


Fig 2 This echocardiogram demonstrates that the saline induced echo reflecting surfaces are localized to the right ventricle (RV) in absence of an intracardiac right to-left shunt

51 and 113 mm Hg for the administered O_2 concentration of 30 per cent 70 per cent and 40 per cent respectively in these cases

Using a Hoffrel ultrasonoscope and a Honeywell fiberoptic strip chart recorder an echocardiogram was recorded with the transducer positioned to display simultaneously the right ventricular outflow tract aortic root aortic valve and left atrium A second recording was made to visualize the right ventricle ventricular septum and left ventricle During the recordings at 25 mm /sec paper speed 2 0 to 3 0 c c of saline or of the patient s own blood was injected rapidly into a central or peripheral vein through an indwelling catheter or cannula The larger volume was used in the older patients The jugular vein was used in six cases the inferior vena cava in five the superior vena cava in five a

The use of saline or blood for ultrasonic detection of a right-to-left intracardiac shunt in the early postoperative patient

Desmond F Duff M B, M R C P I
Howard P Gutgesell, M D
Houston Texas

After repair of a congenital cardiac defect, the reason for early postoperative arterial hypoxemia is sometimes obscure In these patients arterial normocarbia fails to exclude ventilation-perfusion abnormalities, furthermore, a persistent right to left intracardiac shunt may be overlooked if it occurs in combination with obvious hypoventilation

Although radioactive perfusion scan or selective angiocardiography are reliable methods for the identification of a right to left shunt, the critically ill postoperative patient requires a method which is both noninvasive and available at the bedside

Gramiak and associates[1] demonstrated the property of an intravenously injected bolus of saline, blood, or indocyanine green dye to produce a cloud of echoes detectable by ultrasound in the right heart These echo reflecting surfaces are removed during passage through the lung capillary bed and do not appear in the left heart unless there is a right to left intracardiac shunt [1, 2]

This report concerns the application of this principle in the detection of intracardiac right to left shunts in patients in the early postoperative period

From the Section of Cardiology Department of Pediatrics Baylor College of Medicine and Texas Children s Hospital Houston Texas

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Reprint requests Desmond F Duff M B Pediatric Cardiology Texas Children s Hospital 66?1 Fannin St Houston Texas 7?030

Methods and clinical material

Twenty one patients from 7 weeks to 15 yea of age were studied within 48 hours of intraca diac surgery Thirteen patients had tetralogy of Fallot one transposition of the great arteries and pulmonic stenosis, three had ventricular septal defect, two of whom had pulmonary hypertension and the other infundibular pulmonary stenosis Four patients had pulmonary valve stenosis with intact ventricular septum

Hypoxemia or an inappropriate arterial blood Po_2 for the inspired oxygen concentration as outlined by Shapiro[3] was present in eighteen cases (Fig 1) Three patients had a normal arterial blood Po for the inspired O concentration

The average Pco_2 for the entire group was 34 mm Hg (range 21 to 45 mm Hg) and average pH 7 37 (range 7 25 to 7 50) At the time of the study ten patients were receiving assisted ventilation Five patients while still intubated were breathing spontaneously and receiving additional oxygen at high flow rates administered via a T piece Six were extubated and four of these received oxygen by face mask in varying concentrations

The lung fields by chest roentgenogram were normal in 16 of the 21 patients Two had a small pleural effusion which probably did not significantly alter ventilation or perfusion One patient had a small to moderate pleural effusion with atelectasis of the right lower lobe while two patients had areas of consolidation of the middle and lower lobes of the right lung Although the Pco_2 was 37 37 and 27 mm Hg respectively it is probable that the pulmonary changes contributed to the inappropriate Po_2 response 111

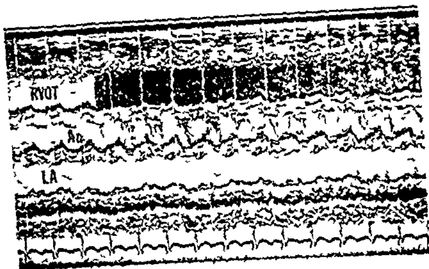


Fig 4A. The echo reflecting surfaces are most densely visualized in the right ventricular outflow tract (RVOT) There are a small number of reflecting surfaces in the aortic root (Ao) but none in the left atrium (LA) This suggests shunting at the ventricular level.

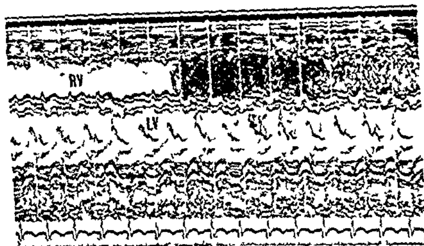


Fig 4B A small number of echo reflecting surfaces appear in the left ventricle (LV) during diastole supporting a right to-left intracardiac shunt at the ventricular level RV = right ventricle

preoperatively a patent foramen ovale had been demonstrated in nine patients and an atrial septal defect in two In each of the 11 patients with atrial shunting the defect was not closed at the time of surgery Two patients in this category had in addition significant lung changes by roentgenogram which may have contributed further to the reduced arterial blood Po_2 Examples of right to left shunting demonstrated by the technique are seen in Figs 3 and 4 Fig 3A shows the echo dense contrast medium filling both right and left ventricles The atrial shunting in this patient is demonstrated in Fig 3B In Fig 4A contrast medium appeared in the right ventricular outflow tract and aorta but not in the left atrium In this same patient (Fig 4B) a very small right to left shunt at ventricular level is evident with the appearance of the reflecting surfaces anterior to the mitral valve during diastole

Discussion

Rapidly injected saline blood or indocyanine green dye produces an echo dense contrast medium with sufficiently different acoustic impedance from the surrounding cardiac structures and normally flowing blood that cardiac chambers can be effectively outlined It has been postulated that this property is a function of microbubbles produced by gaseous cavitation at the catheter tip or which become subtended in the solution as a consequence of the turbulence during rapid injection

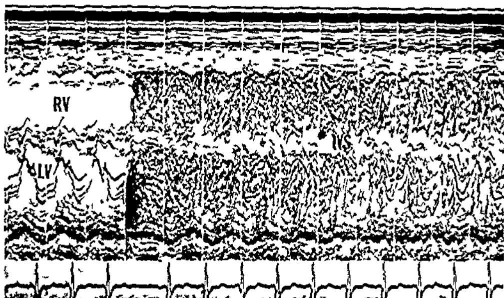


Fig 3A In this echocardiogram of the right (RV) and left ventricle (LV) the echo reflecting surfaces are present in both chambers indicating a large intracardiac right to left shunt The ventricular septum (IVS) is clean suggesting atrial shunting



Fig 3B Appearance of the echo reflecting surfaces in the left atrium (LA) of this same patient demonstrates that the right to left shunt does occur at atrial level *Ao* = aorta *RVOT* = right ventricular outflow tract

peripheral leg vein in two cases and arm vein in three cases

Results

Saline or blood induced echoes appearing in the left atrium systemic ventricle or aorta were indicative of intracardiac right to left shunting The injections were repeated two or three times if required in order to more clearly define or to exclude a right to left shunt Immediately after the injection a dense cloud of echoes appeared initially in the right ventricle in twenty of the 21 cases As expected echoes appeared in the left ventricle in the patient who had had the Mustard procedure for transposition of the great arteries

Visualization of the cloud of echoes contained in the injectate was confined to the right heart in eight cases and an example is shown in Fig 2

Five of these eight patients had a lower than expected arterial blood Po for the administered inspired oxygen concentration while three had a normal Po The cause of the arterial hypoxemia in the five cases was thought to be related to an increase in intrapulmonary shunting The lungs were normal by roentgenogram in four cases A moderate effusion and atelectasis in one of these patients probably also contributed to the reduced Po_2

In thirteen cases an intracardiac right to left shunt was detected by the echo technique, in eleven patients at atrial level and in two at ventricular level At cardiac catheterization

An appraisal of initial QRS forces in left anterior fascicular block

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A frontal plane mean QRS axis directed between −30 degrees and −80 degrees is generally given the designation left axis deviation (LAD) Clinical and pathological studies have correlated such leftward (or superior) axes with a number of conditions including inferior myocardial infarction advancing age and ischemia or fibrosis involving the intraventricular conduction system and/or its contiguous myocardium Several years ago investigations using dogs[1] and monkeys demonstrated that leftward shifts of the QRS axis could be induced by interrupting the more anteriorly located fibers of the left bundle branch system and concluded that pathological changes of similar tissue in man most likely accounted for left axis deviation Building on this framework Rosenbaum and co workers subsequently proposed that the left intraventricular conduction system is anatomically and functionally a bifascicular structure the left bundle branch dividing into clearly separable anterior and posterior fascicles Interruption of the anterior fascicle they felt was responsible for a leftward or superior axis shift and therefore they termed the electrocardiographic pattern of left axis deviation as left anterior hemiblock (LAH) The criteria proposed by Rosenbaum for diagnosing the standard form (Type I) of LAH included a frontal plane QRS axis between −45 degrees and −80 degrees a QRS duration under 0 11 sec and small septal Q waves ≦ 0 02 sec duration in standard Leads I and aV_L Subsequent writings by this group have emphasized the necessary presence of these Q waves as a requirement for the diagnosis of LAH

Over the past few years however we have frequently observed electrocardiograms showing marked left axis deviation in the absence of Q waves in Leads I and aV_L as exemplified in Fig 1 Tracings such as this have led to the obvious question of whether such Qs are in reality an absolute requirement for the recognition of block in the anteriorly located fibers of the LBB We have addressed ourselves in this study to critically assessing the relationship between marked left axis deviation and the presence or absence of these Q waves relating observations made in the present study to currently available electrophysiological and histopathological information

Methods

Standard 12 lead electrocardiograms were collected prospectively in an unselected manner from a hospital electrocardiographic laboratory and categorized according to the frontal plane QRS axis by standard methods Since tracings were taken predominantly on patients with documented or suspected cardiac disease the population in no way represents a normal population Excluded from the study were ECGs showing a QRS duration in excess of 0 10 sec frontal plane QRS axis between +90 degrees and +210 degrees evidence of inferior or lateral wall myocardial infarction (having Q waves of 035 sec or greater in the appropriate leads) preexcitation and junctional rhythm Further ECGs were excluded from analysis in patients under 20 years of age having obstructive pulmonary disease or being pregnant The clinical records chest roentgenograms and when available left ventricular and

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This technique was initially used to verify echocardiographic estimations of cardiac chamber dimensions and to define the source of many intracardiac reflected echoes[1-6] Later the usefulness of contrast studies in the detection of intracardiac shunts and valvular insufficiency was demonstrated[2,5,6] This technique was found to be more sensitive than either indocyanine green dye or oximetry in the detection of intracardiac shunts[1,2] These earlier studies were performed under experimental conditions in animals[5] in human subjects during cardiac catheterization[1-5,6] and in two children in the postoperative period

The occurrence of hypoxemia in the early postoperative period is well recognized following intrathoracic surgery[7] A reduction in diffusion capacity and areas of atelectasis not radiographically detectable lead to an increase in intrapulmonary venous admixture and a fall in arterial blood Po_2[7,8] An intracardiac right to left shunt may present a similar picture not readily differentiated by available techniques In particular, using 100 per cent O_2 will not differentiate an *increase in venous admixture due to intrapulmonary* shunting from that due to intracardiac right to left shunting Mild hypoxemia in the awake patient with a normal cardiac output spontaneous ventilation a normal pH Pco and chest roentgenogram should not delay extubation in the presence of a right to left intracardiac shunt Severe hypoxemia and a right to left intracardiac shunt may indicate inadequate surgical relief of obstruction to pulmonary blood flow and the necessity for further surgical exploration rather than prolonged assisted ventilation with high inspired oxygen concentrations In the absence of an intracardiac shunt these patients may be benefited by the use of positive end expiratory pressure or continuous positive airway pressure (CPAP)[9] By preventing alveolar collapse improved ventilation perfusion ratios are obtained with less physiological shunting and therefore an increase in the arterial blood Po_2 The use of CPAP in the presence of an intracardiac right to left shunt may cause an increase in the degree of shunting and a further fall in Po_2

The demonstration of a cloud of echoes in the left heart following *intravenous injection of* blood or saline, while not quantitative, provides identification of a right to left shunt and an approximation of the size of the shunt

The injection can be made into either a central or a peripheral vein, although a central vein is preferable since the injectate is less diluted when it reaches the right heart and a more rapid injection can be made For the detection of right to left atrial shunting through a foramen ovale or secundum atrial septal defect, a lower limb vein or inferior vena caval injection is more sensitive due to the preferential flow towards the fossa ovalis from the inferior vena cava[2] Injection directly into the right atrium may give a false impression of the magnitude of the right to left shunt as the catheter may be situated close to the fossa ovalis

This technique is simple and safe causing little or no discomfort to the patient The detection of an intracardiac right to left shunt while not excluding additional causes of hypoxemia in particular ventilation-perfusion inequalities or diffusion defects should allow for a more ordered approach to the management of these patients In particular the unnecessary and potentially damaging effects of high oxygen concentrations and/or prolonged assisted ventilation can be avoided

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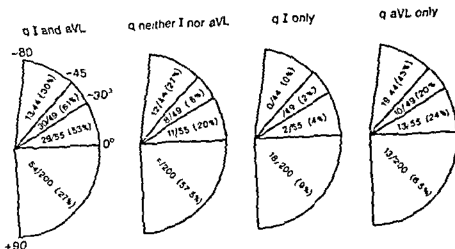


Fig. 2. Graphic display of the fractions (percentages) of tracings in particular axis groupings with Q waves in Leads I and aVL, neither Lead I nor aVL, Lead I alone, and Lead aVL alone. See text for discussion.

test,' $p < 0.001$. Tracings with Q waves in both I and aV_L occur less frequently with QRS axis of 0 degrees to +90 degrees (54 of 200, 27 per cent) than with −1 degree to −80 degrees axis (72 of 148, 49 per cent), $p < 0.001$. Tracings with a Q wave in Lead I but not in aV_L are unusual, being present in only 21 of 348 (6 per cent), all but three of these 21 having a QRS axis in the normal range of 0 degrees to +90 degrees. Tracings with Q waves in aV_L but not in Lead I occurred less frequently (13 of 200, 6.5 per cent) with a QRS axis of 0 degrees to +90 degrees than with an axis of −1 degree to −80 degrees (42 of 148, 28 per cent), $p < 0.001$. It is evident, therefore, that septal Q waves of up to 0.02 sec. duration are more frequently present in tracings with a QRS axis of −1 degree to −80 degrees than in those with a QRS axis of 0 degrees to +90 degrees.

Tracings in the extreme LAD range (−45 degrees to −80 degrees) exhibit marked variability in their initial vectors, Q waves occurring in aV_L alone in 43 per cent, in both Leads I and aV_L in 30 per cent, and in neither Lead I nor aV_L in 27 per cent. However, tracings in the −1 degree to −44 degrees axis group more commonly have Q waves in Leads I and aV_L (57%) than in aV_L alone (22 per cent) ($p < 0.001$) or in neither Lead I nor aV_L (18 per cent) ($p < 0.001$). When the −1 degree to −44 degrees section is dissected into −1 degree to −30 degrees and −31 degrees to −44 degree ranges, it is seen that tracings with Q waves in Leads I and aV_L are only slightly more common in the −31 degree to −44 degree group than in the −1 degree to −30 degree group (61 per cent versus 53 per cent, $p = 0.20$), and that tracings with Q

Table I. *Relationship of Q waves to the occurrence of left ventricular hypertrophy (LVH) and anteroseptal or anterior wall myocardial infarction (MI) in tracings with QRS axis −45 degrees to −80 degrees*

Q waves in Leads	*LVH*	*MI*
I and aV_L	3 of 13 (23%)	5 of 13 (38%)
aV_L alone	0 of 19 (0%)	1 of 19 (5%)
Neither I nor aV_L	0 of 12 (0%)	2 of 12 (17%)

waves in neither Lead I nor aV_L and in aV_L alone are about equally common in both axis groups ($p = 0.31$ and 0.35, respectively). Thus, in the axis range −1 degree to −80 degrees, the presence of Q waves does not appear to be directly related to the degree of left axis deviation.

Table I looks at the frequency of left ventricular hypertrophy (LVH) and septal and/or anterior myocardial infarction (MI) as related to the Q wave patterns in tracings in the −45 degree to −80 degree axis grouping. *None* of these tracings had ECG criteria for *both* LVH and MI. LVH was present in three of 13 (23 per cent) tracings with Q wave in Leads I and aV_L, but was absent in all of 12 tracings with Q wave in aV_L only. MI was present in five of 13 (38 per cent) tracings with Q waves in both Leads I and aV_L, in two of 12 (17 per cent) tracings with Q waves in neither Lead I nor aV_L, and in only one of 19 tracings with Q waves in aV_L alone. It appears, then, that the majority of tracings in all Q wave categories have neither LVH nor septal and/or anterior infarction, suggesting that such processes play at most

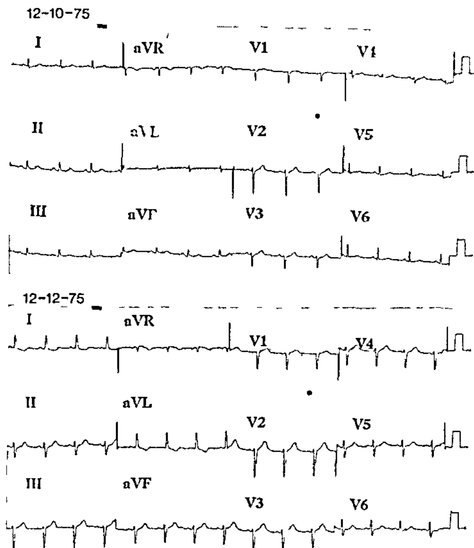


Fig 1 Preoperative tracing of Dec 10 1975 shows a normal QRS axis of about +60 degrees QRS duration of 0 08 sec Q waves in neither Lead I nor aV_L slow precordial r wave progression and borderline ST segment abnormalities and is identical to tracings dating back to September 1975 Postoperative tracing of Dec 12 1975 fulfills most of Rosenbaum s criteria for left anterior hemiblock in that there has been a leftward shift of QRS axis to about −45 degrees mild widening of the QRS to 0 09 sec diminution in precordial r wave amplitude and appearance of large S waves in Leads V and V but there is no change in the initial 0 02 sec vector and Q waves are absent from Leads I and aV The operation performed was saphenous vein aortocoronary bypass to the left anterior descending coronary artery

coronary cineangiograms and autopsy material were examined in an effort to eliminate cases with inferior and/or lateral myocardial infarction unusual chest cage deformity or obesity

Electrocardiograms were grouped according to the QRS axis in the following way −45 degrees to −80 degrees (44 patients considered to manifest extreme left axis deviation) −31 degrees to −44 degrees (49 patients) −1 degree to −30 degrees (55 patients), and 0 degrees to +90 degrees (200 patients those considered to manifest an essentially normal QRS axis) Each tracing was examined for the presence of Q waves in Leads I and aV_L, these ranging from minute size up to 0 02 sec, and were further categorized as to the presence of such Qs in both Leads I and aV_L Lead I only Lead aV_L only and in neither Leads I nor aV_L

Results

Fig 2 displaying the distribution of Q waves in the different axis groupings makes several noteworthy points The majority (115 of 200 57 5 per cent) of tracings with a QRS axis between 0 degrees and +90 degrees have Q waves in neither I nor aV_L while this circumstance occurs in only a minority (31 of 148 22 per cent) of tracings with an axis between −1 degree and −80 degrees The difference in frequency between these groups is statistically significant using the two proportion

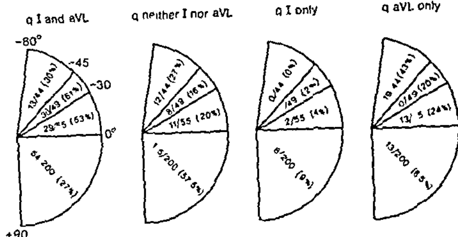


Fig 2 Graphic display of the fractions (percentages) of tracings in particular axis groupings with Q waves in Leads I and aVL neither Lead I nor aVL Lead I alone and Lead aVL alone See text for discussion

test) $p < 0.001$ Tracings with Q waves in both I and aV_L occur less frequently with QRS axis of 0 degrees to +90 degrees (54 of 200 27 per cent) than with −1 degree to −80 degrees axis (72 of 148 49 per cent) $p < 0.001$ *Tracings with a Q wave in* Lead I but not in aV_L are unusual being present in only 21 of 348 (6 per cent) all but three of these 21 having a QRS axis in the normal range of 0 degrees to +90 degrees Tracings with Q waves in aV_L but not in Lead I occurred less frequently (13 of 200 6.5 per cent) with a QRS axis of 0 degrees to +90 degrees than with an axis of −1 degree to −80 degrees (42 of 148 28 per cent) $p < 0.001$ It is evident therefore that septal Q waves of up to 0.02 sec duration are more frequently present in tracings with a QRS axis of −1 degree to −80 degrees than in those with a QRS axis of 0 degrees to +90 degrees

Tracings in the extreme LAD range (−45 degrees to −80 degrees) exhibit marked variability in their initial vectors Q waves occurring in aV_L *alone in 43 per cent in both Leads I and* aV_L in 30 per cent and in neither Lead I nor aV_L in 27 per cent However tracings in the −1 degree to −44 degrees axis group more commonly have Q waves in Leads I and aV_L (57%) than in aV_L alone (22 per cent) ($p < 0.001$) or in neither Lead I nor aV_L (18 per cent) ($p < 0.001$) When the −1 degree to −44 degrees section is dissected into −1 degree to −30 degrees and −31 degrees to −44 degree ranges it is seen that tracings with Q waves in Leads I and aV_L are only *slightly more common* in the −31 degree to −44 degree group than in the −1 degree to −30 degree group (61 per cent versus 53 per cent $p = 0.20$) and that tracings with Q

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a minor role in determining the presence or absence of Q waves of ≦ 0.02 seconds duration in Leads I and aV_L in tracings with QRS duration ≦ 0.10 seconds. Postmortem examination in three and biplane left ventricular cineangiocardiograms in another six of these 44 patients corroborated the electrocardiographic evidence of either presence or absence of MI.

Discussion

Although a leftward and superiorly directed mean frontal plane QRS axis may be the consequence of a variety of factors, including inferior wall myocardial infarction, chronic obstructive pulmonary disease, obesity, and pregnancy, general agreement exists as to the belief that a frontal plane axis of between −45 degrees and −80 degrees may also result from some form of block in the left bundle branch (LBB) and/or its intraventricular branches. In fact, the extreme LAD occurring in some tracings of LVH is attributable to a conduction abnormality induced by concomitant myocardial fibrosis and not to the LVH *per se*.[1] A number of workers have provided support for the hypothesis that a QRS axis in this range may be evoked by interruption of impulses usually carried in the anterior-superior fibers of the left bundle branch.[1-4] This form of conduction block has been termed "left anterior hemiblock (LAH)" by Rosenbaum and associates and "left anterior fascicular block (LAFB)" by a more recently convened committee of recognized electrocardiographers.[1] In classifying clinical status with LAD, Rosenbaum and co-workers[8] attributed marked LAD to obesity, stocky build, and pregnancy in some patients (Type II LAH), to emphysema in others (Type III LAH), and to severe LVH in others (Type IV LAH). The *remaining majority (53 per cent) of patients were* said to have standard (Type I) LAH as an explanation for their left axis deviation in which "There was invariably a Q wave in Leads I and aV_L. . . . The Q wave in Lead I was always small, of normal appearance, and never wider than 0.02 sec." Rosenbaum and colleagues' more recent communications *are explicit in requiring the* presence of Q waves in Leads I and aV_L for the diagnosis of the standard type of LAH, stating that the absence of such Q waves excludes LAH as a cause of left axis deviation.

Our observations prompted us to question the criterion that Q waves in Leads I and aV_L are indispensable for the electrocardiographic diagnosis of LAFB, and we approached this problem by exploring the relationship between QRS axis and coexistent Q waves in Leads I and aV_L, attempting to interpret these relationships in the context of currently available anatomic and electrophysiologic studies of the cardiac conduction system.

The presence or absence of Q waves in Leads I or aV_L relates to the initial 20 msec of ventricular activation, which under normal circumstances in man and dog comes about by essentially simultaneous depolarization of three left ventricular endocardial sites: (1) the central left side of the interventricular septum, (2) the posterior paraseptal area about one third the distance from the apex to base, and (3) a basally located area of the anterior left ventricular wall just below the attachment of the mitral valve.[13, 14] Most electrophysiologists concur that the specialized bundle branch fascicular system initiates ventricular activation at these three sites synchronously, yet disagree to some extent as to which fibers of the conduction system are responsible for initial ventricular depolarization. Rosenbaum and colleagues[8] point out that the initial impulse arrives at the left side of the interventricular septum about 0.01 sec before the right side, due primarily to the longer conduction time in the right bundle branch as compared to the anterior and posterior fascicles of the LBBB, and that this asynchrony in arrival time accounts for normal left to right septal depolarization. In LAH, according to this group, the posterior fascicle is solely responsible for the initial QRS impulse, thereby shifting the 0.01 to 0.02 sec vector inferiorly and to the right in the frontal plane, resulting in the appearance of small Q waves in Leads I and aV_L and small r waves in Leads II and III.

In contrast, the histological observations of Demoulin and Kulbertus[?] and the combined anatomic and electrophysiologic studies of Uhley,[16] Medrano and associates,[?] and Gallagher and co-workers[1] suggest that the left bundle *branch system is trifascicular (rather than having* only the anterior and posterior branches as suggested by Rosenbaum and colleagues), the third fascicle being directed along the interventricular septum, coursing between and interconnected with the anterior and posterior fascicles.

This more complex designation of the left intraventricular conduction system is more in concert with the aforementioned electrophysiologic observations of Durrer and associates[19] demonstrating initial electrical activity simultaneously at three points in the left ventricular myocardium * and with the anatomic studies of Massing and James who found neither a discrete bi- nor trifascicular LBB system but rather a diffuse splay of conduction fibers eminating from the main left bundle branch in a fan like fashion with irregular separations between multiple fiber groups. Although Rosenbaum and colleagues reported the development of new Q waves upon sectioning the left anterior division of the left bundle branch, other groups have found that the initial depolarizing forces generally remained unchanged when the area they defined as left anterior fascicle was experimentally interrupted and that additional interruption of septal ramifications of the LBB was required to produce a rightward shift of the initial 20 msec forces.

The findings of the present investigation can be interpreted in the light of these experimental and histopathological observations. Firstly, we found that Q waves up to 0.02 sec duration in both Leads I and aV_L were more prevalent in tracings with left axis deviation −1 degree to −80 degrees (69 per cent) than in those with a normal QRS axis 0 degrees to +90 degrees (27 per cent). Hence one might reasonably conclude that this slightly greater prevalence of Q waves in the presence of left axis deviation due to left anterior fascicular block could be accounted for on the basis of pathological involvement of the left anterior fascicle and/or septal ramifications of the left bundle branch. In concert with this hypothesis are the histologic autopsy findings of Demoulin, Simar and Kulbertus that patients with electrocardiograms fulfilling Rosenbaum's criteria for left anterior fascicular block had dense fibrosis scattered throughout the left bundle branch system seldom limited to the anterior fascicle. In approximately one half of their cases the anterior subdivision was neither totally interrupted nor more severely damaged than the remainder of the left intraventricular conduction fibers.

Secondly, we found that tracings with extreme leftward axes of between −45 degrees and −80 degrees show a striking variability in the presence or absence of septal Q waves, Qs being present in both Leads I and aV_L in 30 per cent, in aV_L alone in 43 per cent, and in neither Lead I nor aV_L in 27 per cent. Presumably the left axis deviation in these cases was the consequence of left anterior fascicular block since other identifiable causes were excluded. This suggests that although the initial 20 msec QRS vector may be altered in left anterior fascicular block, initial rightward directed forces—i.e., Q waves in Leads I and aV_L—are neither an invariable nor preponderant finding, a postulate which is in accord with the previously noted electrophysiological studies demonstrating failure to induce septal Q waves in the production of isolated LAD by interruption of the left anterior fascicle. These data also agree with the findings of Fernandez and colleagues in which LAD appearing during coronary angiography was unassociated with a predictable change in the direction of the mean initial 0.02 sec QRS vector, and of Kulbertus and associates who found in a vectorcardiographic study of tracings showing LAD that the mean 0.01 sec QRS vector was leftward in 45 per cent of cases, rightward in 40 per cent, and directed principally in an anteroposterior direction in 15 per cent, while the 20 msec vector was leftward in fully 87 per cent of the instances. Additionally relevant are the autopsy observations of patients with *incomplete left bundle branch block* (defined as absence or disappearance of septal Q waves, mildly widened QRS with initial slurring or notching, and delay of onset of the intrinsicoid deflection) showing the frequent appearance of degenerative changes within the left bundle branch system.

We conclude that conduction defects involving the anterior fascicle of the left bundle branch system may be manifested electrocardiographically in a variety of ways:

1. There may be mild to extreme degrees of left axis deviation when there is partial or complete interruption of conduction in the anterior fibers or fascicle of the LBB, the more extreme LAD suggesting more extensive interruption of such fibers.

* According to this construct, normal initial rightward directed septal Q waves result primarily from left-to-right septal depolarization via the septal fibers and activations due to the anterior and posterior branches are in the opposite direction and tend to neutralize each other.

2 The left axis deviation may be accompanied by Q waves in Leads I and aV_L when pathologic process involves additionally the septal subdivisions of the LBB or when such Q waves were present before the development of LAD

3 Left anterior hemiblock (or left anterior fascicular block) *may exist in the complete* absence of 'septal' Q waves representing either persistence of that initial QRS vector present prior to the development of LAD* or a manifestation of disease in the left bundle branch system, *oftentimes termed incomplete LBB Until* correlative studies of human hearts define more clearly the relationships between electrocardiographic and pathological changes, it would seem reasonable after excluding other causes of LAD to *make an electrocardiographic diagnosis of left* anterior fascicular block on the basis of marked left axis deviation regardless of the direction of the initial QRS forces

Summary

To assess whether it is appropriate to require small Q waves in Leads I and aV_L for the diagnosis of left anterior fascicular block (LAFB) routine electrocardiograms from 348 patients were reviewed Cases with inferior or lateral myocardial infarction pregnancy marked obesity obstructive pulmonary disease or unusual chest cage deformity were excluded We found that tracings with Q waves in both Leads I and aV_L occurred less frequently with a normal QRS axis of 0 degrees to +90 degrees (54 of 200 27 per cent) than with a leftward axis of −1 degree to −80 degrees (72 of 148 49 per cent $p < 001$) Tracings with extreme left axis deviation (LAD) (−45 degrees to −80 degrees) exhibited marked variability in their initial vectors Q waves occurring in Lead aV_L alone in 43 per cent in both Leads I and aV_L in 30% and in neither Lead I nor aV_L in 27 per cent Taken in conjunction with currently available histopathological and electrophysiological *information our findings suggest* that LAFB may occur in the presence or absence of 'septal' Q waves depending on both the direction of initial forces present prior to the development of LAD and on pathological involvement of portions of the left intraventricular conduction system other than the left anterior fascicle Once other recognizable causes of LAD are excluded it would seem reasonable to allow an electrocardiographic diagnosis of left anterior fascicular block to be made on the basis *of marked left axis deviation* regardless of the direction of the initial QRS forces

*Note that Q waves were absent in 58 per cent of tracings with QRS axes of 0 degrees to +90 degrees Many of the patients in this group did however have cardiac disease so that this figure should not be taken as representative of the normal population

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Borderline hypertension versus normotension: Differential response to orthostatic stress*

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Borderline essential hypertension† is present when a person's resting systemic arterial blood pressure (BP) is sometimes above, sometimes below an agreed upper limit of normality and no cause for secondary hypertension can be found. It is common[1,2]; the semi-Gaussian distribution of human blood pressures suggests that borderline hypertensives must constitute a substantial proportion of the 33 million adults estimated to have hypertension in the United States.[3] It is not benign. Borderline hypertensives are more liable than normotensives to develop fixed hypertension.[1,2,4,5] Even without this eventuality, data from The Framingham Study[6] and other studies show that the incidence of vascular complications is multiplied several times in the presence of borderline hypertension, which is also known to cause a definite reduction in life expectancy.[9] Thus borderline hypertension contributes substantially to the incidence of cardiovascular morbidity and mortality in the community.

Experience shows, however, that confirming the diagnosis of borderline hypertension is not always easy. There is often difficulty in deciding whether a person found to have a somewhat raised BP is a borderline hypertensive or is a normotensive reacting to unusual stress.[10] This distinction is important prognostically and in management. The borderline hypertensive may in turn present with a normal BP on occasion and be regarded as normotensive. The circumstances of the examination, the implications of its outcome, the personality, status, and attitude of the examiner, and other ill-defined factors undoubtedly contribute to the actual BP level on any given occasion.

A simple noninvasive procedure that could be used to distinguish borderline hypertensives from normotensives would therefore be very useful. We have studied orthostatic stress for this purpose, partly because of its simplicity and availability, partly because of its physiological importance in everyday life. Earlier studies[11-15] have suggested that hypertensives differ from normotensives in their responses to orthostasis, but these studies are not in agreement on the direction and magnitude of the difference. Also, these studies have all used invasive techniques which are inappropriate for routine clinical use.

The present study was undertaken to evaluate the response to orthostatic stress of borderline hypertensives and normotensives using noninvasive methods. We hoped to determine (1) whether the response of borderline hypertensives differed significantly from that of normotensives and (2) how each patient group responded to two forms of orthostatic stress—static stand and head-up tilt.

Materials and methods

The United States Air Force School of Aerospace Medicine (USAFSAM) provides a clinical consultation service for evaluating referred

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†All subsequent references to "borderline hypertension" imply "borderline *essential* hypertension."

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ambulatory aircrewmen with suspected or manifest medical disorders These disorders though mild early and usually symptomless are potentially serious and thus disqualifying for flying duties All patients in the present study were aircrewmen referred to this service

Blood pressure normality was defined as SBP less than 140 mm Hg DBP 90 mm Hg or less These levels (they are based on current U S Air Force standards) were used to define two patient groups for study The first patient group comprised 23 men with borderline essential hypertension (H) All men in this group were found to have intermittently elevated casual BP levels (purely diastolic in four patients systolic and diastolic in 19 patients) during the present evaluation and (by chart review) at least once at routine examination within the past two years Ten of these men had Grade I and one Grade II hypertensive fundus changes five men had a fourth heart sound one man showed ECG (but not clinical) LVH No more serious hypertensive complications were detected and no other evidence of heart disease was present in these patients All members of the hypertensive group were investigated to exclude causes of secondary hypertension tests of renal function IVP and urine examination for increased catecholamine excretion were carried out in all with more specialized tests of suprarenal function in a few cases when indicated

Men selected for the second patient group (n = 26) were normotensive (N) they had never had an elevated SBP or DBP level recorded either at the present evaluation or at any of their previous annual USAF aircrew medical examinations They were selected from patients referred to our consultation service for a variety of reasons including minor ECG abnormalities non disabling arrhythmias ENT ophthalmic and metabolic disorders Nearly all patients in both groups had records of at least annual BP results over the past decade and in many records covered two decades

Prior to inclusion in the study all patients in both groups were assessed by flight surgeons internists ophthalmologists and ENT consultants with further specialist evaluation if indicated All received an extensive laboratory work up chest abdominal and sinus x rays ECG VCG maximal treadmill exercise test at least five hours of Holter ECG monitoring and spirom

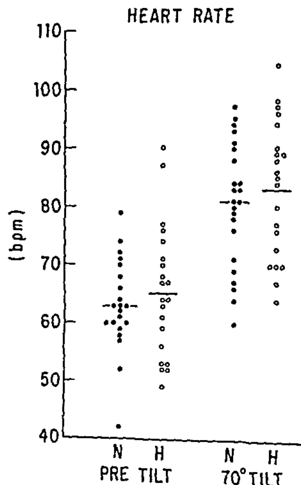


Fig 1 Each point represents the mean heart rate of an individual patient during the pretilt control period or 70-degree tilt period ● = Normotensive N ○ = Hypertensive H

etry No patient in either group had a cardiac conduction abnormality organic cardiac murmur or known coronary artery disease No patient had a history of syncope and none was taking antihypertensive or other drug medication Apart from the selection requirements mentioned no other criteria were used to exclude patients from either hypertensive or normotensive groups A policy of testing consecutive suitable patients as they presented was adopted Of the 49 patients tested results in five (two N three H) were incomplete or otherwise unsatisfactory and were rejected This report describes results from the 44 patients (N = 23 H = 21) whose tests were technically satisfactory

All orthostatic tests were carried out in the early afternoon not less than two hours after a light lunch No prior salt loading or restriction

Borderline hypertension versus normotension Differential response to orthostatic stress*

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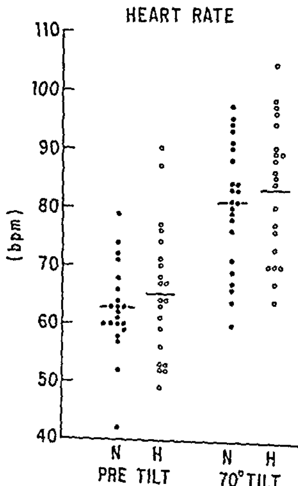


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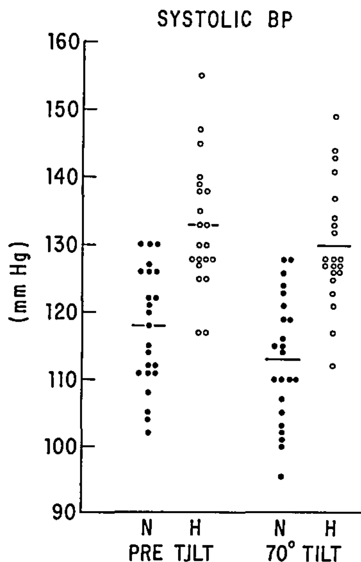


Fig 2 Mean SBPs of individual patients Symbols and periods as in *Fig 1*

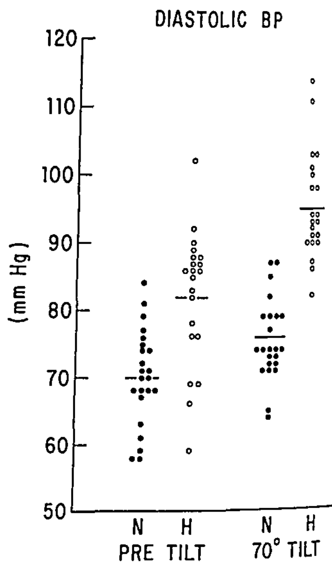


Fig 3 Mean DBPs of individual patients Symbols and periods as in *Figs 1* and *2*

was imposed Ambient temperature was in the range 23 to 26° C The tilt table was of the weight bearing type with footboard 70 degree head up tilt was used in all tilt tests the table taking five seconds to rotate to this angle from the horizontal An armrest supported the right arm at an angle of 45 degrees to the trunk and BP was estimated in this arm by auscultation using a mercury manometer Phase V (disappearance of the Korotkoff sounds) was taken as DBP The BP was measured 1 minute after each change of posture, and thereafter every 2 minutes Heart rate (HR) ECG (Lead X) and respiratory rate were monitored continuously and recorded on a strip chart recorder

The test protocol was divided into two parts (a) static stand and (b) 70 degree head up tilt Immediately following instrumentation the static stand part of the protocol was initiated by five minutes of horizontal rest (prestand control) after being passively tilted to a vertical position the patient stepped to a nearby wall where he stood for a five minute static stand period The tilt part of the protocol followed immediately the patient remounted the tilt table for a 15 minute period of supine horizontal rest (pretilt control) followed by 70 degree head up tilt

Exceptional measures were taken to help the patients feel at ease A small comfortable office was used for all tests telephone and other interruptions were proscribed personnel present were limited to two investigators whose activity was kept to a minimum Conversation was discouraged and seldom occurred These measures seemed to us to be successful the patients appeared calm and relaxed during the tests

For each of the 44 individual patients means for each measurement were computed for the prestand control (5 minutes) static stand (5 minutes) pretilt control (15 minutes) and 5

Table I Group average values and standard deviations for both parts of the protocol

			Static stand part						0° tilt part				
			Pre stand control		Static stand	Δ†	p		Pre tilt control		70 tilt	Δ	p
Heart rate	N	NS	66 ± 8	NS	83 ± 12	17		NS	63 ± 8	NS	81 ± 11	18	
	H		69 ± 12		87 ± 17	18			6 ± 11		83 ± 1?	18	
Systolic BP	N		119 ± 11		116 ± 9	−3	NS		118 ± 9		113 ± 10	−	
	H		134 ± 11		13 ± 8	1	NS		133 ± 9		1?0 ± 9	−3	NS
Diastolic BP	N		0 ± 8		77 ± 7	7			70 ±		76 ± 6	6	
	H		84 ± 10		9 ± 7	13			8 ± 10		9 ± 8	13	
Pulse pressure	N	NS	49 ± 8	NS	39 ± 8	−10		NS	4 ±	NS	38 ± 8	−9	
	H		51 ± 11		38 ± 8	−13			51 ± 11		3 ± 5	−16	

Asterisks against parentheses indicate levels of significance between normotensive (N) and hypertensive (H) values ($p < 0.0$ = , $p < 0.01$ =) †Δ columns show the change between group means in supine control and orthostasis levels of significance of these changes are shown in adjacent columns.

minutes of 70 degree tilt the tilt part data are presented in Figs 1 to 3 (We were concerned about using a mathematical mean to describe the five minutes of orthostasis—static stand or tilt—if in fact the individual had not reached a new steady state within the first minute of this stress Statistical tests applied to the first and third minute values of all measurements detected no significant trend between these times and suggested that the use of mean values was valid) Normotensive and hypertensive group averages and standard deviations were computed (from individual patient means) for each measurement and within each protocol test period group averages were compared using either paired or unpaired t tests as required (See Table 1)

Results

Analysis of means of the two patient groups showed them to be comparable in average age (N 41 years range 30 to 56 years H 41 years range 23 to 52 years) and height (N 179 cm H 181 cm) but the normotensive patients were lighter than the hypertensives (N 76 Kg H 85 Kg $p < .01$) Hypertensive populations tend to be heavier than normotensive ⁴ but the contribution of excessive body weight to hypertension is debatable and data obtained at USAFSAM have tended to minimize its significance There were no significant differences between times of testing length of fasting oral temperatures or room temperatures. The groups (by definition) differed in their casual clinical blood pressure levels

Normotensives vs hypertensives in orthostasis Fig 1 shows the mean heart rates for individual patients in both patient groups first during pretilt supine control then during 70 degree tilt Individual heart rates in both patient groups rose in response to 70-degree tilt The range and distribution of individual heart rates were similar in the two groups for both periods and there was no significant difference between group average heart rates Response of heart rate to supine rest and 70 degree tilt in no way distinguished normotensive from hypertensive patients

Fig 2 presents data for SBP using the same format and symbols as Fig 1 Normotensive patients tended to have lower SBP s than hypertensive patients during both pretilt supine control and 70 degree tilt but only four patients in the hypertensive group showed abnormally elevated SBP s in either period The group average fall with 70-degree tilt was closely similar for both groups There is extensive overlap between individual normotensive s and hypertensive s SBP s during both recumbency and 70 degree tilt and we conclude that SBP in either position is a poor discriminator for borderline hypertension

Fig 3 shows the DBP data In the supine pretilt

control period only two patients in the hypertensive group showed abnormally elevated DBP means Additionally, although the pretilt normotensive group average is significantly ($p < 01$) lower than the pretilt hypertensive group average, the latter is only 82 mm Hg, well within the normal range Finally normotensive patients' mean DBP s tended to be lower than hypertensive patients , but 92 per cent of normotensive and 43 per cent of hypertensive mean DBP s overlapped each other Hence, DBP data from the supine pretilt period did not provide a satisfactory basis for separating the two patient groups

A striking contrast was seen in the DBP response of the two patient groups to 70 degree tilt While patients in both groups showed a tendency for their individual mean DBP s to rise in response to tilt this tendency was much more marked in the hypertensive patients This difference in DBP response resulted in a marked separation of the patient groups, with only seven patients (four normotensive three hypertensive) in the region of overlap All normotensive patients had mean DBP values which remained in the normal range, by contrast 15 (71 per cent) of the 21 hypertensive mean DBP values were now abnormally elevated Group averages confirmed this difference in response, both groups showed a significant ($p < 01$) rise in DBP in response to 70 degree tilt, but the normotensive group rise was significantly less than the hypertensive group rise (6 mm Hg vs 13 mm Hg $p < 01$) In summary, 70 degree tilt resulted in a relatively small rise in the normotensive group average DBP and a much greater rise in the hypertensive group average DBP The difference in individual DBP responses resulted in almost complete separation of the two groups according to their original classification *

Stand vs 70 degree tilt We included the static stand test in our study protocol because of a desire to compare the response to static stand against that to 70 degree tilt static stand offers the obvious economic benefit of not requiring expensive special equipment for orthostatic testing The table presents group average measurement data from both patient groups during both stand and tilt parts of the protocol Group averages for all variables tended to be a little higher during the static stand part than the 70 degree tilt part of the protocol We think this phenomenon is due to the order in which the protocol was carried out Despite this, the similarity of responses (shown in the 'Δ' columns) to static stand and to 70 degree tilt is very striking and was evident in both normotensive and hypertensive groups We believe the response to static standing and to 70 degree tilt is so similar that for practical purposes the procedures are interchangeable Our findings and conclusions on the effects of 70 degree tilt are therefore also applicable to the static stand results

Discussion

Our primary objective has been to determine by noninvasive measurements whether men with borderline hypertension show a distinctive response to orthostatic stress Such a response would be of value in helping to confirm a diagnosis of borderline hypertension in the many patients who, though suspected of this condition are found to have BP levels in the normal range on some or most occasions

Normotensives vs hypertensives in orthostasis The reports by Hickler and associates[16] Taquini and colleagues[1] and Abelmann and Fareeduddin[19] all deal with orthostasis in severe or at least sustained hypertension and are thus not pertinent to the present discussion On the other hand, Sannerstedt[14] reported on a series of 17 young borderline hypertensive patients and 18 normotensive controls the hypertensives had higher heart rates and cardiac outputs in both supine and head up tilt (45 degree) positions These workers also reported that intra arterial BP fell less in the hypertensive patients during tilt than it did in the normotensive patients but we have no information on the specific changes that occurred in SBP and DBP Frohlich and colleagues[11] reported on the intra arterial BP response to 50 degree tilt of a mixed group of 52 hypertensive patients Nearly half had BP responses indistinguishable from normotensive controls In contrast 18 hypertensive patients with mild or early disease were hyperreactive to tilt stress and showed a hypertensive orthostatic

* Enhanced Separation Attempts were made using discriminant analysis statistical techniques, to find measurement variables which might provide additional separation of the two patient groups A total of 23 measurement variables was considered some of these being products of other measurement variables (e g SBP × DBP) Discriminant analysis was applied to each single variable and to each combination of two variables This exercise produced only slight improvement in group separation compared with the use of individual mean DBP s in orthostasis

response defined as greater than 10 mm Hg rise in mean BP Frohlich and associates[15] later compared the orthostatic response of borderline mildly moderately and severely hypertensive patients Their borderline hypertensive patients, who appear comparable to ours showed a hyper dynamic circulatory state characterized by an increase in their peripheral resistance in response to tilt stress which was greater than that of normotensive or of fixed hypertensive patients though the differences did not attain significance Study of published data has therefore led us to the following conclusions regarding the cardio vascular response to tilt of mild or borderline hypertensive patients (a) reports in the literature are not consistent with respect to blood pressure responses (contrast Sannerstedt[4] and Frohl ich[1] [5]) (b) the studies quoted have used invasive measurement techniques which are likely to modify responses to an important degree (Stevens[6]) (c) specific SBP and DBP changes have not been published--previous reports have given only intra arterial mean BP s and (d) none of the measurement variables reported thus far has provided any basis for distinguishing and separating borderline hypertensive patients from normotensive patients

By contrast the present report is unique in identifying a distinctive DBP response to tilt in borderline hypertensive patients which was sufficient to separate most individual hypertensive from normotensive patients This distinction was obtained by using standard noninvasive measurement techniques which are readily applicable in routine clinical care We believe that the DBP differences obtained are real since any artifact associated with sphygmomanometry should apply equally to both patient groups

Static stand vs 70-degree tilt Surprisingly comparison of the effects of standing and of passive tilt on cardiovascular responses has not often been reported Scholz[2] found that in children the two procedures caused changes in SBP DBP PP and HR which were identical in direction and differed only slightly in magnitude Stevens and colleagues[23] and Shvartz[3] reported responses to standing and tilt but used non weight bearing tilt tables Smith and colleagues found notable similarities in the cardiovascular responses of healthy young men to 70-degree tilt and standing no significant differences in average responses of SBP DBP or HR were found. Hyatt and associates[11] employed three orthostatic tests in a bed rest study and found a tendency to a greater rise in HR with tilt than with standing This did not however hold for all the subjects (healthy young men) under all conditions and some individuals showed considerable day to-day variability in response There is therefore little information on the comparability of static stand ing and weight bearing tilt apart from studies of children and young adults and none on hyperten sive patients

Our results suggest that at least when a weight bearing footboard is used cardiovascular responses of young and middle aged normoten sive and hypertensive men to 70-degree tilt and quiet standing for short periods are closely simi lar Our comments on short term orthostatic tilt responses therefore apply also to static standing unless specifically excepted

Further discussion Our findings suggest that orthostatic stress is likely to reveal the presence of diastolic hypertension in borderline hyperten sive patients even when resting supine BP levels are in the normal range Moreover measurement of DBP during five minutes of static standing should according to our findings be as useful for this purpose as tilt table study It is important to realize that measurement of the BP during ortho stasis may reveal surprisingly high diastolic levels in an apparently mild hypertensive or unmask raised DBP in a person who is normotensive during supine rest Omission of BP measure ments during orthostasis may therefore lead to false confidence and to underestimation of the seriousness of a hypertensive problem partic ularly when one considers how much time an in dividual may spend on his feet during the course of a working day It seems possible that the subsequent development of cardiovascular com plications in a proportion of seemingly mild or borderline hypertensive patients may be due to unsuspected and undetected high orthostatic DBP levels

Summary

The effects of 70-degree weight bearing tilt and of static standing were studied in aircrewmen who were assigned to two groups depending on wheth er they were normotensive or had a history of borderline essential hypertension Noninvasive methods were used to collect cardiovascular data During supine rest there was extensive overlap

between members of both groups with respect to all measurements Specifically, all members of the normotensive group and over 80 per cent of the members of the hypertensive group had normal BPs During orthostasis, either 70 degree weight bearing tilt or static standing, patients in the hypertensive group showed a significantly greater rise in DBP than did the normotensive group patients, this resulted in diastolic hypertension in most patients in the hypertensive group while all patients in the normotensive group remained normotensive The difference in magnitude of the rise in individual mean DBP's effectively distinguished the members of the two groups The effects of static standing on all measurements were compared with those of 70 degree weight bearing tilt and were found to be very similar The practical significance of these findings is discussed

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Abolished compensation of cardiac performance after nitroglycerin in patients with ventricular asynergy

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Depressed ventricular function is an important factor in assessing therapeutic consequences in patients with coronary artery disease (CAD) While some authors found a diminished survival rate in CAD patients with prior myocardial infarction[1,2] others reported no influence of myocardial infarction on survival[3] This discrepancy may be partly due to compensatory mechanisms mainly the Frank Starling mechanism which are able to maintain a normal cardiac function in hearts with asynergy after myocardial infarction[3-7] Nitroglycerin (NTG) seems to improve left ventricular function in some coronary artery disease patients[8] This is explained on the basis of an improvement in the balance between myocardial oxygen supply and demand It is therefore interesting how NTG modifies over all and local ventricular function in patients with ventricular asynergy who are compensating their myocardial tissue loss

Methods

Studies were performed in 40 patients undergoing diagnostic catheterization and evaluation of coronary artery disease There were seven females and 33 males with a mean age of 48 2 years (range 26 to 64 years) Each patient gave informed consent for the study There was no systematic selection process for the study it therefore represents a consecutive series Two patients were excluded because of atrial fibrillation during investigation No patient received a premedication

Prior to the use of contrast material heart rate left ventricular and aortic pressures via femoral artery were recorded using a Statham P23Db pressure transducer at the midchest position In mid inspiration (right anterior oblique position) 50 ml of Urografin 76 (meglumine amidotrizoate and Na amidotrizoate) were injected over a period of 2 to 3 seconds with a power syringe while cineangiograms were exposed at 32 frames/sec on 35 mm film Thereafter coronary cinearteriography was performed using selective injections in the right and the left coronary arterial system in multiple right and left anterior oblique views After the last angiogram a waiting period of 20 minutes was allowed to elapse for dissipation of the effect of contrast material Following the waiting period left ventricular pressures were again recorded When left ventricular end diastolic pressure was returned to control levels nitroglycerin 1 6 mg sublingually was given This resulted usually after 5 minutes in a decrease of left ventricular systolic and end diastolic pressure Thereafter ventriculography was repeated Quantitative ventriculography was done using a grid calibration technique and the area-length method[9,27] End diastolic and end systolic volumes were derived from the largest and smallest silhouettes respectively using the apex and the aortic root as reference points The ventriculographic images selected for analysis were from the first four sinus beats following contrast injection

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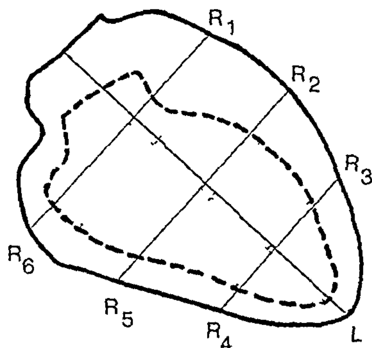


Fig 1 End diastolic and end systolic silhouettes are drawn The hemiaxes during end-diastole and end systole are marked as R through R and L It is evident that a theoretical center of the end diastolic and end systolic area is assumed Both these centers are not identical but became superimposed in calculation

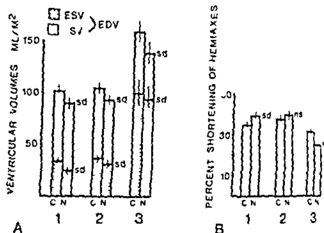


Fig 2A and B *A* Volume data of the three groups studied *B* Shortening of hemiaxes in normal areas of the left ventricle *C* = control conditions *EDV* = end diastolic volume *ESV* = end systolic volume N = after 1 6 mg nitroglycerin sublingually *SV* = stroke volume *ns* = not significant *sd* = significantly different (at least at the 5 per cent probability level) if comparing paired data before and after nitroglycerin *1* = control group *2* = patients with coronary artery disease without asynergy *3* = patients with coronary artery disease with asynergy Values are means plus or minus S E M

No attempt was made to correct to 'true volumes To evaluate ventricular function end diastolic and end systolic volumes (EDV, ESV) stroke volume (SV) and ejection fraction (EF = SV/EDV × 100) were determined To define ventricular asynergy a long axis (L) was drawn from the aortic root to the apex for each end diastolic and end systolic silhouette This axis was divided into hemiaxes by a perpendicular line at the midpoint and perpendicular lines were drawn at the midpoints of these hemiaxes These perpendicular lines from endocardial surface to endocardial surface were called D_1 D_2 D_3 from base to apex as proposed by Dyke and colleagues [10] Shortening of diameters was calculated as diastolic minus systolic divided by diastolic length The lower normal limits (mean minus two standard deviations) for the ejection fraction and for the diameter shortening D_1 D_2 D_3 and L were determined in our laboratory for 32 normal ventricles and are as follows for ejection fraction 53 per cent for D_1 23 per cent for D_2 24 per cent, for D_3 19 per cent and for L 11 per cent A ventricle was termed asynergic when its ejection fraction was below 53 per cent and at least one diameter shortened less than normal The three diameters are divided by the long axis into six hemiaxes (from the long axis to the endocardial surface) These hemiaxes were called R_1 to R The long axis (L) was taken as one axis only because the aortic root does not contract (Fig 1) This approach to quantitate regional ventricular function in ventricular asynergy is derived from Herman and Gorlin [9] The percentage shortening of the projected hemiaxes were used to separate between asynergic and normal areas in ventricles of patients with coronary artery disease Lower normal limits were defined in the above mentioned 32 normal ventricles and are as follows for R_1 = 22 per cent for R_2 = 22 per cent for R_3 = 14 per cent for R_4 = 20 per cent for R_5 = 15 per cent for R_6 = 12 per cent and for L = 11 per cent After the decision if a hemiaxis was normal or asynergic, a mean value was taken for the normal and for the asynergic area of each ventricle In the control group a mean value of the six hemiaxes and the long axis of each ventricle was calculated The 40 patients were divided into three groups

1 A control group consisting of 13 patients who had normal ECG s normal coronary cineartenographies and ventriculographies

2 A group of 16 patients with luminal narrowing of 85 per cent or more of at least one major

Table I

		EDV† (mL/M²)	ESV (mL/M²)	SV (mL/M²)	EF (%)	Per cent shortening of hemiaxes: Infarct area	Per cent shortening of hemiaxes: Normal area	Heart rate (bpm)	LVSP (mm Hg)	LVEDP (mm Hg)
Normals (Group 1)	Control 1	101.9	33.9	68.0	66.6	—	34.7	71.1	131.5	12.6
		±19.9	±10.4	±17.5	±8.5	—	±6.7	±18.2	±18.1	±3.6
	NTG 1	89.6	25.1	64.5	72.0	—	39.4	75.4	121.8	9.6
		±18.1	±8.3	±15.3	±7.2	—	±5.8	±17.2	±11.9	±3.4
p-values										
NTG 1 vs Control 1		<0.01	<0.01	n.s.	<0.05	—	<0.05	<0.01	<0.01	<0.01
CAD without asynergy (Group 2)	Control 2	105.2	36.7	68.5	65.7	8.6	38.2	9.9	147.6	16.9
		±19.1	±11.3	±11.2	±6.2	±7.1	±6.7	±14.4	±15.7	±6.9
	NTG 2	93.6	31.5	62.1	67.2	10.1	40.2	80.9	126.4	8.9
		±17.0	±12.1	±9.5	±8.4	±7.3	±7.3	±15.6	±16.1	±5.1
p-values										
NTG 2 vs. Control 2		<0.01	<0.01	<0.05	n.s.	n.s.	n.s.	n.s.	<0.01	<0.01
Control 2 vs Control 1		n.s.	n.s.	n.s.	n.s.	—	n.s.	n.s.	<0.05	<0.05
NTG 2 vs NTG 1		n.s.	n.s.	n.s.	n.s.	—	n.s.	n.s.	n.s.	n.s.
CAD with asynergy (Group 3)	Control 3	159.6	100.5	59.0	39.0	6.6	31.5	70.8	131.8	20.9
		±34.8	±43.8	±14.5	±12.5	±4.0	±8.3	±12.3	±16.7	±7.7
	NTG 3	139.3	94.3	44.9	33.[illegible]	6.7	24.9	74.3	113.1	13.6
		±36.9	±41.1	±18.5	±14.0	±4.5	±9.8	±14.[illegible]	±16.7	±5.3
p-values										
NTG 3 vs Control 3		<0.01	<0.05	<0.01	<0.05	n.s.	<0.01	n.s.	<0.01	<0.01
Control 3 vs. Control 1		<0.001	<0.001	n.s.	<0.001	—	n.s.	n.s.	n.s.	<0.05
NTG 3 vs NTG 1		<0.001	<0.001	<0.01	<0.001	—	<0.001	n.s.	n.s.	<0.05

Mean values ± standard deviation

†Abbreviations CAD = coronary artery disease n.s. = not significant EDV = end-diastolic volume ESV = end-systolic volume SV = stroke volume EF = ejection fraction HR = heart rate LVSP = left ventricular systolic pressure LVEDP = left ventricular end-diastolic pressure NTG = after nitroglycerin

coronary branch and with no evidence of asynergy in the control ventriculogram The ECG was normal in 10 patients a subendocardial anterior myocardial infarction (without pathologic Q waves) was present in three and inferior infarction was present in three other patients

3 A group of 11 patients with luminal narrowing of 85 per cent or more of at least one major coronary branch but with evidence of asynergy in the control ventriculogram The ECG revealed an anterior myocardial infarction (with pathologic Q waves) in eight patients and an inferior myocardial infarction in three patients

Statistical significance was accepted at the 5 per cent probability level when using the Student t test for paired and unpaired data

Results

Control conditions The results of the study are summarized in Table I and Fig 2 Patients without asynergy (Group 2) showed no significant difference of all angiographic parameters as compared to the control group ($p > 0.05$) However the left ventricular systolic and enddiastolic pressures were significantly elevated (both $p < 0.05$) in Group 2 The shortening of hemiaxes in normal areas was comparable to normal ventricles ($p > 0.05$ Fig 2) In seven of 16 patients small areas of the left ventricle showed impairment of hemiaxes shortening while the ejection fraction as well as the shortening of diameters remained within normal limits

Patients with asynergy (Group 3) showed larger end diastolic volumes ($p < 0.001$) larger endsystolic volumes ($p < 0.001$) and decreased ejection fractions ($p < 0.001$) as compared to the control group The stroke volume was not significantly different from the control group ($p > 0.05$) Heart rate and left ventricular systolic pressure were normal ($p > 0.05$) while end dia

stolic pressure was elevated in patients with asynergy Shortening of hemiaxes in non infarcted areas of asynergic ventricles was normal as compared to the control group ($p > 0.05$, Fig 2), while asynergic areas showed only minimal shortening

Effects of nitroglycerin

A Control Group Comparison of paired observations in normal patients showed a significant decrease of end diastolic volume ($p < 0.01$) and of end systolic volume after NTG ($p < 0.01$, Fig 2) The ejection fraction increased ($p < 0.05$) while stroke volume remained nearly constant ($p > 0.05$) Left ventricular systolic and end diastolic pressure decreased after NTG (both $p < 0.01$) while heart rate increased ($p < 0.01$) Shortening of hemiaxes increased significantly ($p < 0.05$ Fig 2)

B CAD without asynergy Again a significant decrease of end diastolic and end systolic volume (both $p < 0.01$ Fig 2) was found, however in contrast to the control group the ejection fraction remained unchanged Consequently stroke volume decreased significantly ($p < 0.05$) Heart rate remained unchanged while left ventricular systolic and end diastolic pressure decreased ($p < 0.01$)

C CAD with asynergy As in both other groups end diastolic and end systolic volume decreased significantly after nitroglycerin ($p < 0.01$ resp < 0.05) However while in normal patients end systolic volume after NTG was 74 per cent of control, in CAD patients with asynergy end systolic volume after NTG was only 94 per cent of control both these changes are significantly different ($p < 0.05$) It is therefore apparent that in patients with asynergy reduction of end systolic volume is drastically impaired while reduction of end diastolic volume is normal As a result stroke volume decreased to 76 per cent of control after application of NTG ($p < 0.01$) Shortening of asynergic segments showed no change while shortening of normally contracting segments fell significantly after nitroglycerin ($p < 0.01$) The marked deterioration of pump performance is further reflected by reduced ejection fraction ($p < 0.05$) Heart rate remained unchanged, while left ventricular systolic and end systolic pressure decreased ($p < 0.01$)

Comparison of groups after nitroglycerin No differences between normals (Group 1) and patients without asynergy (Group 2) could be shown regarding angiographic and hemodynamic parameters (Table I)

In patients with asynergy (Group 3) the stroke volume, which was within normal range before nitroglycerin, was significantly decreased after nitroglycerin if compared to Group 1 ($p < 0.01$ Table I) Left ventricular end diastolic pressure was still elevated in Group 3 as compared to Group 1 ($p < 0.05$) Shortening of normally contracting segments in Group 3 was significantly lower as compared to Group 1 ($p < 0.001$)

Discussion

Nitroglycerin produced a significant deterioration of cardiac performance in patients with ventricular asynergy as measured by stroke volume and ejection fraction The deterioration was a result of reduced shortening of normally contracting areas in asynergic ventricles while abnormal areas remained unchanged For the study of ventricular volumes in man some methological problems need further discussion First of all it has to be recognized that the injection of contrast material into the left ventricle induces a temporary depression of cardiac function which is accompanied by an increase of end diastolic volume and pressure [11] Maximal hemodynamic changes occur within three minutes and return to normal within 15 minutes [1 13] For this reason we allowed 20 minutes as a minimum rest period before NTG and proceeded with the study after careful control of left ventricular end diastolic pressure The significant reduction of end diastolic volume after NTG in each group allows the conclusion that the effects of contrast material were no longer effective Another problem is the evaluation of volumes from a single plane angiogram As was shown by Cohn and associates [14] a good correlation exists in patients with asynergy between single plane and biplane angiograms with the exception of some cases Especially the motion of the posterolateral segment can be misinterpreted as outlined by Helfant and coworkers [15] No patient in our group with asynergy had an isolated disease of the left circumflex artery, and the error should therefore be minimal although it cannot totally be excluded Our results of volume data are comparable to those of other investigators [16]

In normal patients NTG produced a decrease of end diastolic and end systolic volume while

stroke volume decreased slightly but not significantly In normal human ventricles Burggraf and Parker[1] using ultrasound found a reduction of end diastolic and end systolic volumes within 2 to 5 minutes accompanied by an increase in heart rate and a decrease of systolic and end diastolic left ventricular pressure Cardiac output remained unchanged while stroke volume fell slightly The decrease in ventricular volumes after NTG was explained by Vatner and colleagues as mediated by the reflex tachycardia because smaller changes occurred after constant ventricular rates It appears however not adequate to explain reduction in heart size after NTG by heart rate changes since heart rate remained unchanged in both CAD groups in the presence of significant reduction in end diastolic volume The slight increase in ejection fraction in our normal group accompanied by an increase of shortening of hemiaxes may be attributable to an increase in contractility mediated by reflex mechanisms or by decreased afterload[1, 20] Within the group of CAD without asynergy as defined by ejection fraction and by diameter shortening the analysis by hemiaxes revealed an abnormal contraction pattern in seven out of 16 patients This demonstrates that asynergy is a problem of quantification It may be concluded that asynergy not detected by the application of diameter shortening is slight and limited to small areas only In these areas changes of wall motion after NTG were inconsistent Sniderman and associates[23] McAnulty and colleagues[4] and Helfant and co workers[5] found comparable results insofar as about 50 per cent of hypokinetic segments showed improved wall motion after NTG We used in this study a dose of nitroglycerin (1 6 mg sublingually) which is above what is usually a therapeutic dose because we know from other studies that doses of 0 4 mg and 0 6 mg [1] are not high enough to produce a regular and significant decline of left ventricular end diastolic volume and pressure in patients with ventricular asynergy However it was the aim of our study to evaluate the effect of nitroglycerin under comparable conditions in normal patients and in patients with coronary artery disease

In patients with ventricular asynergy a significant deterioration of over all and local ventricular function was found after NTG Before NTG an abnormally high end diastolic volume and pressure maintained a normal stroke volume probably as a consequence of the Frank Starling mechanism NTG induced a reduction of both end diastolic volume and pressure which was followed by a significant decrease of shortening in normally contracting areas of asynergic ventricles Consequently stroke volume fell below the respective value in the control group A conclusive explanation in our mind could be that diastolic tension in obviously normal areas was shifted downward and to the left of the Frank Starling curve (resting length-tension) which resulted in a reduced work output Another possible explanation must be considered based on experiments of Forman and co workers[21] They found a decrease of shortening of endocardial layers in poststenotic areas after NTG and offered the explanation of a decrease of blood flow as a consequence of decreasing perfusion pressure In our series of patients with asynergy only two had additional critical stenoses supplying normally contracting areas It is therefore not possible to apply this explanation to our results Lee and associates[22] investigating a group of CAD patients (irrespective of ventricular asynergy) found a considerable decrease of stroke volume after application of NTG accompanied by a decrease of mean circumferential fiber shortening rate Williams and colleagues[2] found a significant decline of cardiac output and arterial perfusion pressure after application of sublingual nitroglycerin in patients with acute myocardial infarction and elevated left ventricular filling pressures They concluded that the reduction of myocardial oxygen needs is offset by the unfavorable hemodynamic deterioration with decreasing coronary blood flow NTG reduces myocardial oxygen consumption in enlarged ventricles by reducing ventricular volumes and wall tension[17, 2, 23, 24] If we assume that marginal ischemic zones may be present in asynergic ventricles NTG should have improved their wall motion[4, 23] however this was not found In addition NTG did not diminish end systolic volumes in enlarged ventricles to the same extent as in normal ventricles despite equally decreased afterload It cannot be excluded that the reduced fiber shortening of normal areas will result in a decrease of myocardial oxygen consumption However in these areas an oxygen sparing effect of NTG apparently is not needed On the other hand NTG reduced systolic pressure and stroke volume considerably We conclude that NTG sublingually brings out

this dilemma of medical therapy in patients with ventricular asynergy congestive symptoms may improve but pump function deteriorates because the Frank Starling compensation is disturbed

Summary

Left ventricular function was studied in 40 patients before and 20 minutes after 1 6 mg of sublingual nitroglycerin Thirteen patients had no evidence of heart disease, 16 had obstructive coronary artery disease (85 per cent luminal narrowing) without ventricular asynergy and 11 had obstructive coronary artery disease with ventricular asynergy (as a consequence of prior transmural myocardial infarction) Before and after nitroglycerin end diastolic volume, end systolic volume ejection fraction, and shortening of hemiaxes was comparable in the control group and in patients without asynergy Before nitro glycerin end diastolic volume, end systolic vol ume and end diastolic pressure were significantly elevated in patients with asynergy as compared to controls while stroke volume was maintained within normal limits Normally contracting segments in ventricles with asynergy showed a comparable percentage shortening of hemiaxes as was found in normal hearts After nitroglycerin stroke volume was significantly reduced in asy nergic ventricles as compared to both other groups This was due to reduced shortening of normally contracting segments in ventricles with asynery while shortening in asynergic areas remained unchanged after nitroglycerin The results are explained on the basis of the Frank Starling mechanism An increased diastolic pres sure is needed in enlarged hearts to enable nonin farcted myocardium to shorten The result is a normal stroke volume Nitroglycerin lowers dias tolic pressure to that extent that shortening in noninfarcted segments is significantly reduced resulting in a fall of stroke volume Since no improvement of left ventricular function could be demonstrated *the beneficial effects of nitrogly* cerin are offset by the abolished compensation of cardiac output in ventricles with asynergy

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Hypertrophic cardiomyopathy The heart disease of Friedreich's ataxia*

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Friedreich s ataxia is a familial neuromuscular disorder characterized clinically by spinocerebellar ataxia, loss of deep tendon reflexes, and skeletal deformities Many reports[1-6] have drawn attention to the frequent clinical electrocardiographic and histological evidence of myocardial involvement in this disease, although neither the incidence nor the pathogenesis of the cardiac abnormality have been firmly established

Hypertrophic cardiomyopathy (HCM) or idiopathic hypertrophic subaortic stenosis (IHSS) is an uncommon form of familial myocardial disease which has occasionally been reported in patients with Friedreich s ataxia[7-1] Based on the uncommon prevalence of these two entities their presence in the same patient would be unexpected by chance alone thus suggesting that HCM might be the cardiomyopathy of Friedreich s disease Studies to date, however, have not substantiated this hypothesis possibly reflecting the difficulties involved in establishing the diagnosis of HCM (particularly in the absence of outflow obstruction) by means of standard hemodynamic and angiographic techniques

In the present study we evaluated a group of patients with Friedreich s ataxia by means of echocardiography a technique which has recently been shown to provide a highly sensitive and relatively specific means to diagnose HCM[11] The purpose of the study was threefold (1) to ascertain if patients with Friedreich s ataxia have the typical echocardiographic features of HCM (2) to determine whether hypertrophic cardiomyopathy is the specific cardiomyopathy of Friedreich s ataxia and (3) by means of family studies to investigate the inheritance pattern of this disease

Patients and methods

Hospital records from the major teaching institutions of Dalhousie University were reviewed for cases with a discharge diagnosis of Friedreich s ataxia Eleven patients from eight families were available to follow up and agreed to participate in the investigation There were six females and five males with ages ranging from 9 to 30 years (mean 19 years) All had the usual history of onset and progression of symptoms and had at least moderate neurologic disability at the time of study Only patients who had clinically typical features of Friedreich s ataxia were included in the study

Each patient had complete clinical evaluation and a 12 lead electrocardiogram (ECG) Echocardiograms were recorded using a focused 2 25 MHz transducer and a commercially available ultrasonoscope * The output from this instrument was recorded on a multichannel fiber optic recorder†

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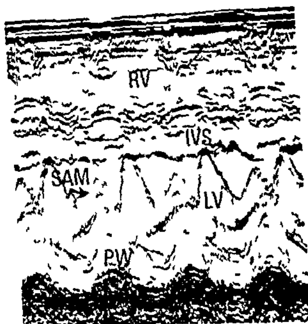


Fig 1 Echocardiogram from patient No 2 showing the systolic anterior motion (*SAM*) of the mitral valve characteristic of obstructive HCM Other abbreviations *IVS* = interventricular septum *LV* = left ventricle *PW* = posterior wall *RV* = right ventricle.

using light sensitive paper Standard scanning techniques were employed with particular emphasis placed on delineation of the interventricular septum and posteriorbasal aspect of the left ventricular free wall Measurements included septal and posterior left ventricular free wall thickness at end diastole and left ventricular end diastolic and end systolic internal dimensions From these data calculations were made of the ratio of septal to posterior wall thickness and the per cent systolic change of the diastolic internal dimension

Results

Patients

Clinical features The pertinent clinical and ECG features of the 11 patients are shown in Table I Although all had significant impairment of exercise capacity secondary to their neurologic deficit none had definite cardiovascular symptomatology Two patients (Nos 1 and 2) had clinical findings suggestive of typical IHSS with rapid carotid upstrokes prominent left ventricular impulses atrial sounds and long systolic murmurs accentuated by Valsalva maneuver Two additional patients (Nos 3 and 4) had prominent apical impulses and atrial sounds without systolic murmurs These four patients (Group A) all had abnormal ECGs with voltage and repolarization criteria for left ventricular hypertrophy The remaining seven patients (Group B) had essentially normal clinical exami

Table I Clinical and electrocardiographic data

Patient	*Age*	*Sex*	*Ataxia*	*Murmur*	*ECG*
Group A					
1	24	F	4+‡	+	LVH
2	11	F	2+	+	LVH
3	18	M	3+	0	LVH
4	25	M	2+	0	LVH
Group B					
5	29	F	4+	0	T↓
6	11	F	2+	0	T↓
7†	24	M	4+	0	n
8†	15	M	3+	+	n
9†	9	M	2+	0	n
10	30	F	4+	0	n
11	9	F	2+	0	n

Siblings †siblings.
‡Ataxia is graded 1 (minimal) to 4 (severe)
Abbreviations ECG = electrocardiogram LVH = left entricular hypertrophy n = normal T↓ = T wave inversion in the inferior and lateral precordial leads

Table II Echocardiographic data

Patient	Age	Dd (mm)	Ds (mm.)	% Change	IVS (mm)	LVPW (mm)	IVS/LVPW	SAM
Group A								
1	24	37	18	51	17	9	1 9	+
2	11	30	16	47	19	10	1 9	+
3	18	41	27	34	23	10	2.3	0
4	25	45	25	44	15	10	1 5	0
Group B								
5	29	42	28	33	11	9	1.2	0
6	11	36	23	36	8	8	1 0	0
7	24	43	27	37	8	7	1 1	0
8	15	46	28	39	8	8	1 0	0
9	9	24	16	33	5	5	1 0	0
10	30	42	24	42	10	9	1 1	0
11	9	36	25	30	8	7	1 1	0

Abbreviat ons Dd = diastolic internal dimension Ds = systolic internal dimension IVS = interve tricular septum LVPW = left ventricular posteri r wall SAM = systolic anterior motion of the anterior mitral leaflet.

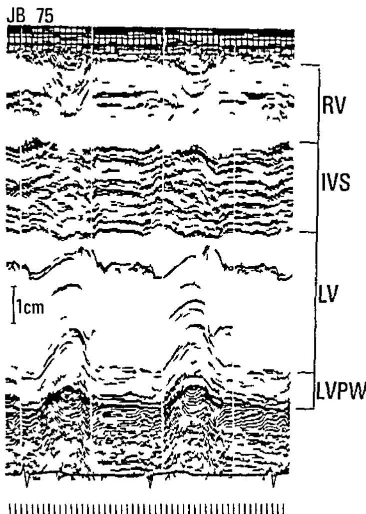


Fig 2 Echocardiogram from patient No 3 showing typical features of non obstructive HCM The interventricular septum (*IVS*) is grossly thickened and relatively immobile when compared to the left ventricular posterior wall (*LVPW*) Other abbreviations as in *Fig 1*

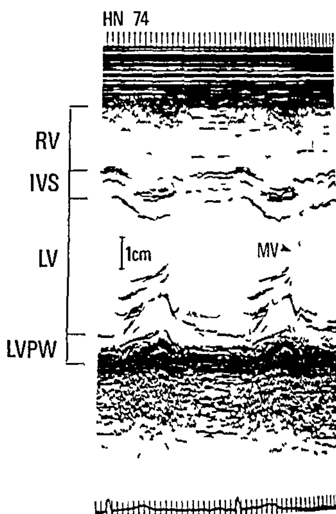


Fig 3 Echocardiogram from patient No 10 Note the normal thickness and mobility of the IVS compared to the posterior wall *MV* = mitral valve other abbreviations as in *Figs 1 and 2*

nations Five of these had normal ECGs whereas two had T wave inversions in the inferior and lateral precordial leads No patient had clinical evidence of pulmonary hypertension or signs of right ventricular failure

Echocardiographic features The findings on echocardiography are shown in Table II All 11 patients had normal or decreased diastolic and systolic left ventricular internal dimensions with normal or increased per cent change with systole Group A patients all had moderate to gross hypertrophy of the interventricular septum with only minimal or no increase in thickness of the posterior wall The resultant septal to posterior wall thickness ratios ranged from 1 5 to 2 3 all being in excess of the 1 3 value previously suggested as diagnostic of HCM [13] Two patients (Nos 1 and 2) had systolic anterior motion (SAM) of the anterior mitral leaflet (Fig 1) a feature previously reported to occur in patients with HCM and basal or provokable left ventricular outflow obstruction [15] Fig 2 shows the echocardiogram from patient No 3 which in addition to the obvious discrepant hypertrophy of the septum reveals other characteristic features of HCM Thus the septum has little or no systolic motion or thickening whereas the posterior wall demonstrates excessive systolic function [16]

The patients in Group B all had normal septal and posterior wall thickness and consequently normal septal to wall thickness ratios Fig 3 is the echocardiogram from patient No 10 which shows normal septal thickness and function as well as normal systolic change in the left ventricular internal dimension

First degree relatives

Clinical features All first degree relatives (including both parents) of patients Nos 1 2 4 5 and 11 were evaluated In addition one parent of

patient No 3 was available for study Neurological assessment was normal in all cases and with the exception of one subject with poorly controlled systemic hypertension none had historical or clinical evidence of cardiac disease The ECGs were within normal limits in all cases

Echocardiographic features Technically satisfactory echocardiograms were obtained in 16 of the 17 subjects All had normal septal and posterior wall thickness and normal values for left ventricular dimensions and function

Discussion

Although HCM has been previously reported in patients with Friedreich's ataxia [1, 2] the frequency of this association has been unknown Using echocardiography as the diagnostic tool we have found that approximately one third of a group of Friedreich patients had features which are indistinguishable from those observed in typical HCM Since we did not find clinical or echocardiographic evidence of heart disease in the absence of this abnormality the data suggest that HCM is the specific cardiomyopathy of classical Friedreich's ataxia

Although previous workers have proposed such an hypothesis [10] the lack of a sensitive and specific method for establishing the diagnosis of HCM (particularly in the non obstructive form) has made this conjectural In recent years echocardiography has proved extremely useful in this regard primarily as a result of the important observations of Henry and co workers[11] and Abbasi and colleagues[ ] These workers noted that patients with HCM were characterized echocardiographically by discrepant hypertrophy of the ventricular septum when compared to the posterobasal aspect of the left ventricular free wall a feature which is independent of the presence or absence of outflow obstruction On the basis of their experience Henry and associates suggested that a septal to posterior wall thickness ratio of 1 3 or greater (asymmetric septal hypertrophy) is diagnostic of the IHSS disease spectrum although subsequent studies have proved this to be not entirely accurate [ ] Thus some patients without HCM particularly those with marked right ventricular pressure overload will also have asymmetric septal hypertrophy Attention to other characteristic echographic features however enables the diagnosis of HCM to be made with assurance in the vast majority of cases Thus systolic anterior motion of the anterior mitral leaflet [15, 20] an anteriorly positioned mitral valve [21] decreased excursion and systolic thickening of the septum [14, 22] and increased systolic thickening of the left ventricular free wall[14] all add diagnostically important information Of the patients in this study with abnormal septal to posterior wall thickness ratios (Group A) two had systolic anterior movement of the mitral valve and all four had characteristic abnormalities of mitral valve position and wall motion Thus by available echocardiographic criteria these four patients had typical HCM The echographic data are supported by the ECG evidence of left ventricular involvement and by the absence of clinical signs of right ventricular pressure overload as a possible explanation for the asymmetric septal hypertrophy

The finding that seven of the 11 patients with typical features of Friedreich's ataxia (Group B) had no echographic evidence of cardiac disease is consistent with previous observations Thus symptoms referable to the heart have been noted in only approximately 50 per cent of cases[ ] with a similar proportion suspected of dying from cardiac cause[ ] Abnormalities detected on physical examination generally have been reported in a lower incidence[ ] whereas ECG changes may be present in up to 90 per cent of patients [ ] Of those with ECG abnormalities approximately 50 per cent of reported cases had ventricular hypertrophy [ ] whereas the majority of the remaining group had rhythm disturbances or T wave changes limited to the inferolateral leads The significance of this latter change is unknown but it is perhaps noteworthy that the two patients in our series with isolated T wave inversions had normal clinical examinations and normal echocardiograms Although the group is too small to make definite conclusions this observation suggests that patients with only T wave changes either do not yet have the fully developed myocardial disease or perhaps that this ECG abnormality is unrelated to the development of cardiomyopathy in Friedreich's ataxia Conversely in our series ECG evidence of left ventricular hypertrophy was specific for HCM

We did not feel justified in performing hemodynamic and angiographic investigation in our patients and except for the previously cited case reports [1, 12] very little information in this regard is available from the literature Ruschhaupt and

colleagues[10] studied five patients (in addition to their case report) and found angiographic evidence of left ventricular hypertrophy in all and a provokable left ventricular outflow tract gradient in one. Cote and Élias [3] reported basal or provokable left ventricular outflow gradients in three of nine patients and Thoren[4] has commented on the small thickened left ventricles in his two patients undergoing angiography. Although these studies were obviously performed in very selected patients the results do confirm the hypertrophic and occasionally obstructive nature of this cardiomyopathy.

Whereas the reported incidence of clinical evidence of cardiac involvement has been generally in the order of 50 per cent, most histologic studies in Friedreich's ataxia have reported myocardial abnormalities.[5] The major features are muscle fiber hypertrophy and increased interstitial fibrous tissue, changes which are also characteristic, although not specific, for HCM.[1] Even the intimal hyperplasia of small intramyocardial coronary vessels noted in patients with Friedreich's ataxia[3,5] and believed by several workers to be important in the pathogenesis of the myocardial changes[5] may be observed in the hearts of patients with HCM.[1] It is noteworthy, however, that the two most characteristic pathologic abnormalities of HCM, namely discrepant septal hypertrophy and muscle fiber malalignment,[24] have not, to our knowledge, been noted in hearts from Friedreich's patients. Although it would be desirable to have pathologic correlation of our echographic results, such data are presently unavailable.

Thus the reported clinical, electrocardiographic, hemodynamic and myocardial histologic features of Friedreich's ataxia are compatible with our echocardiographic findings and lend support to our conclusion that HCM is the specific heart disease of classical Friedreich's disease. However, it seems clear from previous data as well as our echocardiographic findings that not all patients with Friedreich's ataxia have the cardiomyopathy. As is apparent in Table I there was no association between the presence of HCM and either the age of the patient or the severity of the neurologic disturbance. These observations raise the possibility that Friedreich's ataxia may be genetically heterogenous, with HCM being a distinguishing feature between two genetically distinct forms. If this was so, then one would expect that HCM in Friedreich's ataxia families would run true, that is, all affected family members would either have HCM or fail to develop it. Although our data tend not to support this thesis (patient No. 4 had HCM whereas his sibling was unaffected), the study group is too small to draw definite conclusions.

The results of this study may have particular relevance to the question of the pathogenesis of HCM. Although recent reports indicate that this disease by itself is inherited as a dominant trait,[1,6] our findings suggest that recessive transmission can also occur. Moreover, the presence of HCM in four of 11 patients with Friedreich's ataxia clearly indicates that both the myocardial and neurologic abnormalities represent pleiotropic effects of the same deleterious gene. This implies that HCM may be a form of neurogenically induced heart disease, a possibility previously suggested because of independent observations. Thus, Polani and Moynahan, noting the occasional association between lentiginosis and HCM, postulated that both the myocardial and pigment abnormalities could be due to dysfunction of embryonic neural crest elements. Based on this observation plus the infrequent coexistence of HCM with pheochromocytoma and neurofibromatosis, Goodwin[1] has suggested that the disorder might be the result of either excess production of catecholamines or abnormal responses to these substances by developing cardiac muscle. More recently we have demonstrated histochemical and histologic abnormalities of voluntary muscle in patients with HCM;[2] in several cases these changes were of a nature usually considered specific for neurogenically induced muscle damage. Although the majority of patients with HCM do not have clinically apparent evidence of neurologic disease, these associations occur much more frequently than expected by chance. Thus it seems probable that the disease we recognize as HCM is multicausal but that its pathogenesis is closely linked to genetically determined abnormalities of neuronal structure of function.

Clinical implications of our findings are speculative at present. However, since approximately 50 per cent of patients with Friedreich's ataxia die from cardiac cause,[5] the prognosis might be expected to be influenced considerably by the presence of HCM. Although currently available therapy for this cardiomyopathy is not optimal

early recognition and management (particularly in the obstructive group) may provide considerable improvement in the quality and perhaps duration of life It seems reasonable therefore to recommend echocardiographic assessment of patients with Friedreich's ataxia particularly in those with clinical and/or ECG evidence of myocardial involvement

Summary

Recent case reports have drawn attention to the occasional association of hypertrophic cardiomyopathy (HCM IHSS) with Friedreich's ataxia In order to ascertain the frequency of this association 11 patients (ages 9 to 30 years) with Friedreich's ataxia were assessed clinically and by means of echocardiography a technique recently shown to provide a highly sensitive and relatively specific means to detect HCM Two patients had clinical features suggestive of obstructive HCM and these plus two others had electrocardiographic (ECG) evidence of left ventricular hypertrophy All four had echocardiographic features of HCM (septal to posterior wall thickness ratios ranging from 1 5 to 2 3) with or without evidence of outflow tract obstruction The remaining seven patients had normal clinical examinations and normal echocardiograms although two had T wave abnormalities on ECG Sixteen first degree relatives of these patients were evaluated in the same manner none had clinical ECG or echocardiographic evidence of myocardial disease Thus approximately one third of this group of patients with Friedreich's ataxia had HCM This finding suggests that HCM is the specific cardiomyopathy of classical Friedreich's ataxia and that both the neurologic and myocardial defects represent pleiotropic effects of the same deleterious gene Since approximately 50 per cent of patients with Friedreich's ataxia die from cardiac cause early detection and management of HCM may favorably alter their prognosis

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Absence of Wedensky effect in man

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The Wedensky effect is excitation by a subthreshold stimulus after previous excitation by a strong stimulus[1] This phenomenon described in a frog nerve-muscle preparation by Wedensky and reproduced in the dog Purkinje fiber by Goldenberg and Rothberger[2] is different from Wedensky facilitation in which a blocked impulse lowers the threshold for stimulation below the block

The Wedensky effect has been used to explain certain ectopic beats[3,4] and electrocardiographic observations[5-7] But the evidence for Wedensky effect in man rests in the main upon demonstration by Castellanos and associates[8] of propagated responses from subthreshold right ventricular stimulation when preceded by strong stimuli in two of seven patients with complete heart block Because of bradycardia late diastolic depolarization at the site of subthreshold stimulation was not excluded Furthermore recent evidence from patients with bradycardia[11] suggests an extended duration of supernormality with late diastolic reappearance of the supernormal period in some This is an alternate explanation for the results of Castellanos and colleagues[8]

We therefore sought to validate the existence of Wedensky effect in man We measured the quantitative relationship between progressively increased strengths of prior stimulation and concomitant reductions in threshold for subsequent beats In addition we attempted to elicit the Wedensky effect in patients studied at normal heart rates by programmed exploration of diastole with subthreshold stimuli preceded by strong stimuli

Methods

Ten patients were studied in the postabsorptive state The study was performed only if programmed ventricular extrastimulation was shown not to provoke sustained tachycardias Clinical and electrocardiographic characteristics of the patients studied are listed in Table I

Pacing was performed via a bipolar pacing catheter with interelectrode distance of 1 cm fluoroscopically guided to achieve stable anatomic and threshold position at the right ventricular apex

Stimulation was provided by a two channel Grass S88 stimulator with separate SIU5 isolation units Extrastimulation was digitally determined by a Quartec APS 2 programmer Stimulation thresholds for propagated responses were determined as the voltage of a rectangular impulse 2 msec in duration delivered with an output impedance of 250 ohms Ventricular extrastimuli (S_2) were applied after eight beats of ventricular drive (S_1) at 100 beats/minute Threshold for extrastimulation was the minimum voltage consistently yielding a propagated response at a given coupling interval (S_1-S_2) Because extrastimulus threshold was determined after continuous pacing drive threshold was determined as the minimum voltage required for >90 per cent capture as stimulus strength was diminished from that yielding complete capture Only those studies were utilized in which identical thresholds during continuous pacing were obtained at initiation and completion of measurements

Recordings were made with an Electronics for Medicine DR 12 oscilloscopic recorder The precise time of stimulation was determined from a

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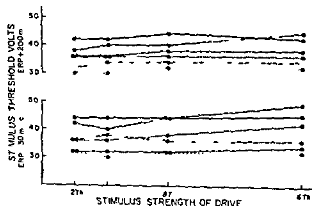


Fig 1 The thresholds (Th) for ventricular extra stimuli applied 200 msec after the effective refractory period (ERP upper panel) and 30 msec after the effective refractory period (lower panel) are indicated on the y axis. The x axis refers to the strength of stimulation used to establish the ventricular drive that preceded the extrastimulus. Stimulation strength for drive is indicated in terms of the threshold (Th) for ventricular pacing. There is no reduction in threshold for extrastimulation at higher drive stimulus strengths. Although there is a trend in fact for increased drive strength to increase threshold for extrastimulation, this is of borderline statistical significance

variability in determination of right ventricular refractory periods in our laboratory

The threshold for post drive beats was not reduced by progressive increase in the stimulus strength of ventricular drive. As indicated in Table II no patient demonstrated a reduction in threshold for early or late extrastimulation. In fact Fig 1 illustrates that the threshold for extrastimulation actually increased by an average of 0.2 volts ± 0.1 S.E.M. when drive stimulus strength was 16 times threshold. This increase however achieved borderline statistical significance ($p < 0.05$) only for late extrastimuli (S S = effective refractory period + 200 msec).

Diastole was scanned with subthreshold extrastimuli (90 per cent threshold) in patients 4 to 10 while drive stimulus strength was strong (16 times threshold). There were no propagated responses that could be interpreted as Wedensky effect at any coupling interval in any patient.

Discussion

Although described in in vitro models the Wedensky effect is more difficult to explain than the other of Wedensky's phenomena, Wedensky facilitation and inhibition. The latter two can be viewed as the superimposition of the effects of current conducted in concealed or electrotonic fashion. However the propagated effect of the strong stimulus of Wedensky effect would not be expected to be the strong stimulus itself but as shown in this study the propagated response. Since the response to a strong stimulus appears to be the same as that to a just sufficient stimulus it is difficult to understand how that strong stimulus could effect responses to later stimulating events. Nonetheless the concept of Wedensky effect has remained viable in clinical electrocardiography.

Castellanos demonstrated propagated responses to late subthreshold stimuli in two of seven patients studied. These responses occurred when the heart had been previously excited by strong stimulation at a different site and were consistent with Wedensky effect. Unfortunately values for the thresholds and the subthreshold stimulus strengths utilized were not reported and we cannot be certain that the propagated responses did not occur because of subtle variations in the threshold independent of the strong shock. The likelihood of threshold variation was compounded by utilization of pacemaker catheters positioned in the pulmonary artery and thus not fixed in stable positions.

Castellanos patients (as well as Goldenberg's Purkinje fibers) were bradycardic because of complete heart block and because the strong stimulation was applied at slow rates. They were thus subject to spontaneous late diastolic depolarization. This reduction in resting membrane potential could lower threshold for pacing independently of the strength of prior stimulation. It has recently been demonstrated in bradycardic patients that the supernormal period can extend well beyond the T wave or reappear later in

Table I Clinical features of patients studied for Wedensky effect

Patient No	Age (years)	Sex	Diagnosis	HR (bts/min)	Electrocardiogram	Medications
1	45	M	CAD†	94	Anteroseptal MI VEBs (460) VT	None
2	59	M	CAD	78	Inferior MI	None
3	21	M	Syncope normal coronaries	72	Normal	None
4	49	F	Angina normal coronaries	90	Normal	None
5	63	M	CAD	87	Normal	None
6	50	F	Angina normal coronaries	92	Normal	None
7	65	F	CAD	72	VEBs (400 460)	Propranolol 160 mg/day
8	50	M	CAD	62	Sinus arrest	None
9	51	M	CAD	70	Anteroseptal MI LAH	None
10	47	M	CAD	75	Normal	Propranolol 160 mg/day

Cardioactive medications other than nitrates received within 3 days of study
†Abbreviation CAD = coronary artery disease HR = heart rate LAH = left anterior hemiblock MI = myocardial infarction VEBs = ventricular ectopic beats (coupling intervals indicated in msec) VT = ventricular tachycardia

Table II Thresholds for ventricular extrastimulation

Coupling interval	Patient no	Thresholds for extrastimuli (S) at various strengths of ventricular drive (S_1)			
		S = 2xTh	S = 4xTh	S = 8xTh	S = 16xTh
S S = ERP +30 msec	1	3 2 V	3 0 V	3 2 V	3 2 V
	2	3 2 V	3 2 V	3 2 V	3 4 V
	3	4 2 V	4 0 V	4 4 V	4 8 V
	4	3 6 V	3 8 V	3 6 V	3 6 V
	5	4 4 V	4 4 V	4 4 V	4 4 V
	6	3 6 V	3 6 V	3 8 V	4 2 V
S S = ERP +200 msec	1	3 0 V	3 0 V	3 2 V	3 2 V
	2	3 6 V	3 6 V	3 8 V	3 8 V
	3	3 8 V	4 0 V	4 0 V	4 4 V
	4	3 2 V	3 4 V	3 4 V	3 4 V
	5	4 2 V	4 2 V	4 4 V	4 2 V
	6	3 6 V	3 6 V	3 6 V	3 6 V

Abbreviations ERP = effective refractory period S = drive stimulus S = extra stimulus Th = threshold V = volts

ventricular electrogram recorded from the pacing catheter at 40 500 Hz with a paper speed of 100mm/second

Thresholds for extrastimuli (S) were determined as a function of the preceding stimulus strength (S_1) in six patients (patients 1 to 6 of Table I) Initially effective refractory periods were determined as the longest S_1 S interval at which an extra stimulus of twice S threshold failed to propagate Effective refractory periods were determined at increasing drive stimulus strengths (S_1 = 2 4 8 and 16 times threshold) The threshold for extrastimuli applied early in diastole (S_1 S = effective refractory period + 30msec) and late in diastole (S_1 S = effective refractory period + 200msec) were then determined at S_1 = 2 4 8 and 16 times threshold (See Table II)

In three of the above patients and four additional patients (patients 4 to 10 of Table I) the thresholds for extrastimulation at 30 msec intervals throughout diastole were determined while drive stimulus strength was twice threshold These patients were then tested for propagated beats representing Wedensky effect during a strong drive with stimulus strength of 16 times threshold by scanning diastole at 10 msec intervals with extrastimuli at 90 per cent of the threshold for each S_1 S interval as previously determined when drive was only twice threshold Subthreshold stimulation at the 90 per cent level was chosen because the variability of threshold determinations generally was 0 2 volts (> 5 < 10 per cent of threshold)

Results

Effective refractory periods were not altered by increasing the stimulus strength of ventricular drive In all patients effective refractory period remained constant within 20 msec the expected

The pathophysiologic basis of acute coronary insufficiency Observations favoring the hypothesis of intermittent reversible coronary obstruction

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As a clinical entity acute coronary insufficiency is characterized by episodes of angina pectoris provoked by little or no exertion and separated by relatively longer asymptomatic intervals It is a temporary condition which typically either subsides in a matter of days or evolves into myocardial infarction or sudden death The emergence of this syndrome commonly is believed to signify a new permanent obstruction in a major coronary artery which compromises blood flow to the extent that even basal nutritional requirements of the myocardium are only marginally satisfied If this theory regarding the pathogenesis of acute coronary insufficiency is correct in the majority of cases one would expect to find (1) signs of myocardial hypoxia at rest (2) very low coronary reserve and (3) relatively few coronary collaterals at first with subsequent collateral development in response to the hypothetical new coronary obstruction in the patients whose rest pain eventually resolves

An alternative theoretical pathologic basis of acute coronary insufficiency is intermittent reversible coronary artery obstruction the process resolving in some patients but in others finally leading to permanent obstruction and infarction If the episodes of angina were produced by transient ischemia myocardial O supply and coronary reserve during the asymptomatic intervals would be comparable to that of patients with stable chronic coronary disease In the absence of a new permanent coronary occlusion one would expect to find collaterals distributed in their usual relation to the existing coronary disease The rate of occlusion in the immediate future however might be high

Prospective studies of medical vs coronary bypass surgical therapy for acute coronary insufficiency and for chronic angina pectoris provided us with an opportunity to evaluate these two alternative hypotheses This report compares patients with acute and chronic clinical states with respect to their myocardial O_2 supply coronary reserve and distribution of coronary disease and collaterals Follow up angiography in patients allotted to medical therapy allows comparison of subsequent progression of coronary obstruction and collateral development between the acute and chronic patient groups

Methods

During the 3 1/2 year period ending July 1975 52 patients were admitted to the Portland Veterans Administration Hospital with acute coronary insufficiency meeting all of the following criteria new or accelerated angina continued episodes of rest angina despite 24 hours of bed rest and reversible ischemic ST or T wave ECG changes The present report is based on the 42 patients (mean age 52 years) who consented to participate in a prospective randomized study of medical vs urgent coronary bypass therapy and who were found to have operable coronary disease

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diastole The latter may merely represent diastolic depolarization but is an alternative manner of explaining propagation of otherwise subthreshold late stimuli

In this study we sought to quantitate the relationship between the strength of the strong stimulus and the ensuing reduction in threshold Establishing linear or otherwise quantitative continuum to the relationship would indicate that altered threshold occurred because of the strong stimulus independent of other variables Measurements in patients who were in sinus rhythm were performed at a normal rate, helping to exclude diastolic depolarization or late super normality A search for propagated beats from subthreshold stimulation after strong stimuli was systematically made after previous determination of expected threshold at all intervals of diastole Thus supernormality, diastolic depolarization and other factors that might be related to the timing of the stimulus were discounted with only the strength of prior stimulation remaining a variable The same electrode position was utilized for both strong and subthreshold stimulation to eliminate the possibility of summation of impulses from separate sites which would more closely resemble a model of Wedensky facilitation than effect

In this study we were unable to demonstrate a reduction in threshold because of strong prior stimulation We were unable to elicit Wedensky effect when threshold changes related to the timing of the stimulus were excluded We thus accumulated no evidence for Wedensky effect in the right ventricle of man

It should be emphasized that our patients were studied at normal heart rates and were for the most part free of arrhythmias None had late ectopic beats or clinical evidence suggesting a Wedensky effect Thus the existence of such an effect as a pathologic state was not excluded However there as yet appears to be insufficient evidence for invoking the Wedensky effect as an electrophysiologic property to explain unexpected beats in the human heart

Summary

Ten patients all in sinus rhythm and without conduction defects were examined for Wedensky effect during right ventricular pacing at 100 beats/minute Thresholds for pacing stimuli and programmed extrastimuli were determined separately Thresholds of post drive beats early and late in diastole (effective refractory period + 30 msec and + 200 msec) were determined in 6 patients When the strength of drive stimulation was increased (2,4,8, and 16 times threshold), the threshold for post drive beats was not reduced in any patient In seven patients, threshold for extrastimuli at all intervals throughout diastole were determined while drive stimulus strength was twice threshold These patients were then tested for beats representing Wedensky effect with a strong drive stimulus strength of 16 times threshold by scanning diastole with subthreshold extrastimuli (90 per cent of the threshold for each coupling interval as previously determined when drive was only twice threshold) Propagated responses were not observed in the seven patients so tested These results suggest that the strength of prior stimulation does not alter the threshold for subsequent excitation Wedensky effect was not demonstrated in this study to be a source of excitability or ectopy in man

Among many others the assistance of Mr George Raudenbush has been most invaluable in completion of this study

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Table IV Myocardial O_2 supply at rest

	ACI patients (n = 34)	Chronic angina patients (n = 3?)
Heart rate (min)	?5 ± 10	?0 ± 11
Mean arterial pressure (mm Hg)	91 ± 15	9? ± 11
Po a (mm Hg)	65 3 ± 9 2	75 ? ± 8 6 *
Po cv (mm Hg)	21 3 ± 2 4	?1 1 ± 2 2
Lactate a (mM)	0 54 ± 0.?1	0 5? ± 0 19
Lactate (a cv/a)	0 21 ± 0 14	0 19 ± 0 ?2

Values represent mean ± S D Abbreviations a = arterial, cv = coronary venous

Po was not determined in these chronic angina patients, and the values for chronic angina represent 90 other patients reported by us elsewhere

P < 0 05 P < 0 001 ACI vs chronic angina by unpaired t test

reached Observations consisted of heart rate brachial artery pressure and paired arterial and coronary venous blood samples analyzed for pH Po hemoglobin and lactate concentration

The significance of differences was judged by the Fisher Exact Probability Test (Tables I to III) or by non paired (Tables IV and VI) or paired t test (Table V) Differences with p > 0 05 were considered not significant

Results

The distribution and extent of coronary artery disease did not differ significantly between acute coronary insufficiency and chronic stable angina patients (Table I) as found previously by others Most patients had occlusion or significant stenosis in two or more major coronary arteries Left main stenosis was more common in acute coronary insufficiency but the difference was not significant

The presence of collaterals (Table II) was related to the severity of arterial obstruction and there were no significant differences between acute coronary insufficiency and chronic angina patients In both groups collaterals were usually not visualized with stenosed arteries especially when the stenosis was mild and were virtually always present with completely occluded arteries

The subsequent progression of coronary disease and collaterals is shown in Table III In four of 17 patients stenoses which were present during acute coronary insufficiency had progressed to complete occlusion within the four month interval prior to repeat angiography Two of these patients showed ECG evidence of asymptomatic myocardial infarctions during the same interval All four developed new collaterals to the distal vessel which had not been present during the initial angiography whereas only one developed new collaterals without a new occlusion None lost collaterals Among the 24 patients with chronic stable angina only one developed a new complete occlusion without apparent infarction The occlusion was accompanied by collateral development and change in collaterals was uncommon in patients without new occlusions

In four patients coronary angiography also had

Table V O_2 administration in acute coronary insufficiency patients (n = 29)

	Room air	O inhalation
Heart rate (min)	?6 ± 10	3 ± 10
Mean arterial pressure (mm. Hg)	89 ± 17	93 ± 21
CaO_2 (ml./100 ml)	17.9 ± 1.5	19 9 ± 1 5
C(a-cv)o (ml./100 ml)	11.5 ± 1.5	12.7 ± 2 0
Po a (mm Hg)	65 ± 9.2	?48 ± 142
Po cv (mm Hg)	21.2 ± 2 45	23 5 ± 4 0?
pHa	?39 ± 0 0?4	7.38 ± 0 030
pHcv	7.3? ± 0 022	?34 ± 0 029
Lactate a (mM)	0 54 ± 0 ?2	0.54 ± 0 21
Lactate (a-cv/a)	0 22 ± 0 14	0 23 ± 0 21

Values represent mean ± S D

Abbreviations C = concentration a = arterial cv = coronary venous.

P < 0 05 P < 0 001 O vs. room air by paired t test

Table VI Angina provoked by pacing

	ACI patients (n = 21)	Chronic angina patients (n = 31)
Heart rate (min)	1?1 ± 20	118 ± 18
Lactate a (mM)	0 53 ± 0 20	0.53 ± 0 18
Lactate (a-cv/a)	0 14 ± 0 2?	0 11 ± 0.21

Values represent mean ± S D

Table I Distribution and severity of coronary artery disease (≥ 50% stenosis or occlusion)

	ACI patients (n = 42)	Chronic angina patients (n = 40)
No of arteries diseased		
1	8	4
2	11	16
3	23	20
Arteries diseased		
Left main	8	2
Left anterior descending	32	36
Left circumflex	30	31
Right	32	29

ACI = acute coronary insufficiency

Table II Coronary collaterals

	Percent narrowing	No of arteries	Collaterals	Contralateral collaterals
ACI patients (n = 42)	50-75	26	1	1
	75 95	34	4	4
	100	35	34	24
Chronic angina patients (n = 40)	50-75%	16	0	0
	75 95	39	4	4
	100	41	41	27

by angiographic criteria (only four patients were inoperable) Coronary angiography was repeated after four months in 17 of the 20 patients allotted to medical treatment (three declined) Details of the prospective study plans have been published

Comparative data were obtained from 49 patients (mean age 52 years) admitted to the same hospital during approximately the same period for severe chronic angina with a stable course for the preceding six months (New York Heart Association functional class III) Forty of these patients participated in a prospective randomized study of medical vs surgical therapy for chronic angina and nine who were not suitable surgical candidates subsequently engaged in a medically supervised program of exercise conditioning Details of the latter nine patients have been published Coronary angiography was repeated (mean interval 7 months) in 15 of the 17 patients randomly assigned to medical therapy

Table III Progression from stenosis to occlusion

	ACI patients	Chronic angina patients		
		Total	Randomized study	Exercise conditioning
No of patients	17	24	15	9
No of stenosed arteries	26	36	23	13
Progression to occlusion	4	1	1	0
With new collaterals	4	1	1	0
New collaterals without occlusion	1	1	1	0
Loss of collaterals	0	1	1	0

(all who consented) and in all nine patients (mean interval 4 months) undergoing exercise conditioning

All patients were in research protocols approved by an institutional human rights committee and informed consent was obtained prior to each invasive procedure

Selective coronary angiography was performed by the Judkins technique obtaining multiple projections with 35 mm cine and large cut films Significant stenosis was defined as 50 per cent or greater reduction in arterial diameter (i e 75 per cent or greater reduction in cross sectional area) The presence of collaterals was judged by definite opacification distal to a complete occlusion or from a contralateral injection distal to a stenosis or occlusion

To study myocardial O_2 supply a pacing catheter was positioned in the coronary sinus midway between its ostium and the left border of the cardiac silhouette Patients were not premedicated Observations were made at rest and in some patients also during angina induced by atrial pacing and/or during inhalation of 100 per cent O_2 by mouthpiece or loose fitting face mask (the different methods of administration explains the high S D for arterial blood P_{O_2} Table V) The sequence of rest and O_2 inhalation was random whereas pacing always was last Pacing began at a heart rate of 80 to 100 per minute and increased by increments of 10 beats per minute until angina pectoris occurred or a rate of 150 per minute was

increased collaterals or recanalization of previously occluded arteries as an explanation for the disappearance of rest pain that did occur over the same interval Instead new collaterals appeared only in response to new proximal occlusions

The results summarized in Table III suggest that stenosed arteries in patients with acute coronary insufficiency are especially susceptible to occlusion during the period immediately following the acute phase of their illness The numbers are too small to establish this point statistically unless one also takes into account the interval at risk between angiographies Four of 26 stenosed arteries became occluded within four months in acute coronary insufficiency patients an occlusion rate per stenosed artery-months of 1/26 which is less than the rate of 1/209 in our chronic angina patients ($p < 0.05$) Expressed in the same way the occlusion rates among other groups of patients with chronic angina who also were systematically re studied were 1/100 (V S Mathur personal communication) among patients randomly assigned to medical therapy and 1/200-300 among patients participating in an exercise program Comparison to progression rates among patients who were selected for repeat angiography[ ] rather than systemically restudied in a prospective design would be less valid

During asymptomatic intervals between attacks of rest angina myocardial O_2 and lactate extraction and the paced heart rate required to provoke angina were not different for acute coronary insufficiency patients than for patients with chronic angina evaluated by the same techniques (Tables IV and VI) This observation is inconsistent with the theory that the myocardium is constantly on the verge of hypoxia The substantial coronary reserve as assessed by induced tachycardia implies that the episodes of chest pain and ischemic ECG signs that occur in acute coronary insufficiency patients at rest must be brought about by intermittent reversible phenomena of considerable magnitude occult increase in myocardial metabolic rate or transient decrease in coronary blood flow We did not intensively investigate our patients during ischemic episodes in the Coronary Care Unit Others have shown that attacks of angina at rest in these patients often but not invariably are accompanied by tachycardia or systemic hypertension[ ] The increase in myocardial work brought about by these hemodynamic changes in itself might be responsible for provoking myocardial hypoxia in some patients Possibly even more important these changes might reflect some generalized systemic phenomenon also directly involving the coronary circulation e g vasoconstriction or platelet aggregation mediated by transiently augmented sympathetic activity A mechanism of this type could explain the occasional presentation of this syndrome in patients without demonstrable coronary atherosclerosis[ ]

We believe that our findings support the following hypothesis concerning the pathophysiology underlying the acute coronary insufficiency syndrome The attacks of angina unprovoked by exertion are initiated by transient reversible events superimposed on severe coronary atherosclerosis rather than by a new fixed obstruction Intracoronary platelet aggregation seems especially likely although we have no direct evidence of this As each of the repeated vascular events is reversed the ischemic pain subsides and the patient regains his previous sizable margin of coronary reserve The process usually resolves in days or weeks leaving no substantial residual change in the underlying coronary obstructive disease, and in this case the ischemic episodes are not sufficiently persistent to induce new collaterals In some patients however one of these arterial obstructions persists long enough to be transformed to a permanent coronary occlusion Then myocardial infarction and/or new coronary collaterals are likely sequelae

It should be presumed that a syndrome with diverse clinical presentations is not likely to have a single pathologic basis The hypothesis proposed here is most tenable for patients with an acute illness of predominantly rest angina It is less satisfactory for those with new angina or acutely increased severity of exertional angina

Summary

Clinical coronary angiographic and myocardial metabolic data were analyzed to test alternative hypotheses for the pathophysiologic basis of acute coronary insufficiency The initial incidence of coronary collaterals was not low in relation to coexisting coronary obstructive disease the early subsequent coronary occlusion rate was high and in asymptomatic intervals

been performed prior to the onset of acute coronary insufficiency (intervals 2½ 3 3 and 4 years) None showed evidence of a new occlusion without collaterals at the time of acute coronary insufficiency *A new occlusion with collaterals* was present in one patient and a new stenosis was present in another

Observations pertaining to myocardial O_2 supply with the patients in the resting state are presented in Table IV Acute coronary insufficiency patients had a slightly higher heart rate and lower arterial blood Po_2 There were no differences in mean values for coronary venous blood Po or myocardial lactate extraction between the two groups of patients Myocardial lactate production at rest was present in three patients with acute coronary insufficiency and in two patients with chronic angina

The effect of inhalation of high O_2 concentration in acute coronary insufficiency patients is shown in Table V There was a slight fall in heart rate and rise in mean artrial blood pressure as observed in other types of patients[8] Arterial O concentration coronary arteriovenous O_2 difference and arterial and coronary venous blood Po_2 increased whereas arterial and coronary venous blood pH decreased slightly There was however, no change in myocardial lactate extraction indicative of any alteration in myocardial O_2 supply or amelioration of resting myocardial hypoxia These results are similar to previous findings in patients with chronic angina pectoris[1, 10]

Table VI shows observations during atrial pacing We were able to provoke angina by pacing in 19 of 21 acute coronary insufficiency patients and in 30 of 31 chronic angina patients The heart rate at which angina occurred and the myocardial lactate extraction during angina were comparable for the two groups of patients The mean heart rate threshold for angina in the acute coronary insufficiency patients was 64 per cent above their mean resting heart rate

Discussion

The opinion presently held by some cardiologists that coronary collaterals are scarce in patients with acute coronary insufficiency is based on rather doubtful evidence Parker and associates[11] reported that retrograde coronary blood flow from selected arteries measured at surgery was less in patients with acute coronary insufficiency than in those with stable angina Their analysis is biased, however, by the fact that in the acute coronary insufficiency patients the blood flow measurements were made in arteries which were specifically selected because they previously had lacked angiographically visible collaterals Fischl and colleagues[7] concluded that angiographically demonstrable collaterals were relatively infrequent in acute coronary insufficiency, but their control group is difficult to accept since the patients were studied under different circumstances at other institutions Several investigators have shown that the presence of collaterals is powerfully influenced by the severity of coronary obstruction[1, 16] For a valid comparison, then the control group should be shown to have equally severe underlying coronary disease Moreover, considering the lack of uniformity in assessing collaterals ideally their presence or absence in both groups should be decided by the same observer We found that among surgical candidates with similar degrees of coronary obstruction collaterals were as common in patients with acute coronary insufficiency as in others Inclusion of the four inoperable patients would not have affected the outcome significantly The incidence of collaterals in our acute coronary insufficiency patients was 40 per cent of 95 partially or totally obstructed arteries compared to 38 per cent of 42 arteries found by Fischl and co workers[7] or an incidence of 64 per cent of our 42 patients compared to 47 per cent of 64 patients reported by Scanlon and associates[6] and 48 per cent of 56 patients reported by Conti and colleagues These are not very large differences considering the possible variations in patient groups and definitions of collaterals

If the symptoms characterizing acute coronary insufficiency were caused by a new fixed coronary stenosis or occlusion which has not yet been compensated adequately by collateral development we would expect to find relatively few coronary collaterals on the initial angiograms Discovery of the usual relationship between collaterals and obstructive disease in our patients does not support this pathologic explanation for the syndrome Admittedly in many patients the symptoms began two weeks or more prior to the initial angiograms and some collaterals could already have developed Nevertheless the attacks of rest angina were still occurring at the time of angiography and did subside subsequently Repeat angiography four months later did not show

Diagnosis of right ventricular infarction Experimental study through the use of body surface isopotential maps

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Clinical recognition of right ventricular infarction is rather difficult and has been diagnosed accurately only at autopsy [1] Though right ventricular infarction is rather rare its clinical recognition is quite important in patient management because it has a tendency to cause severe complications[2] such as right ventricular rupture pulmonary embolism and mural thrombosis In conventional electrocardiograms of right ventricular infarction patients some cases have no Q waves and some cases demonstrate Q waves in Leads II III and aV_f though this finding is also observed in the cases of left ventricular diaphragmatical wall infarction that is no specific findings consistent with right ventricular infarction can be achieved from conventional electrocardiograms

The use of body surface isopotential maps (referred to below as maps for short) provides significant diagnostic information that is not available in conventional electrocardiograms

The purpose of this study is to determine if there are consistent characteristic map patterns associated with right ventricular infarction or not

Methods

Coronary artery occlusion Twelve mongrel dogs weighing from 8 to 12 kilograms were anesthetized with thiamylal sodium (20 mg /Kg) and maintained by artificial respiration Then the chest of each dog was opened by an incision at right fifth intercostal space and myocardial infarction was caused by ligation of the branch of the right coronary artery

One week after ligation each heart was isolated for direct observation and myocardial infarction was confirmed by histological studies

From the original 12 cases six cases were selected in which the infarcted region was limited to the right ventricular anterior free wall and which did not include the septal portion or the diaphragmatic free wall The maps and analysis presented in this study are based on these six cases and references to the dogs refer to these cases

Recording and displaying maps The procedure for recording and displaying maps has been reported in detail previously [4,5] Briefly mapping was based on the record of unipolar lead electrocardiograms taken through the use of needle electrodes attached to 85 lead points of each dog s chest surface (59 on the anterior and 26 on the dorsal) in a supine position under anesthesia and artificial respiration From these electrocardiograms through the use of a minicomputer system a body surface isopotential map was obtained every 1 5 msec throughout the entire time course of ventricular depolarization

All dogs had two series of maps based on the electrocardiograms recorded before and a week after the ligation

Epicardial sequence of the ventricular activation To detect the intraventricular conduction

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during the acute illness, myocardial hypoxia was infrequent and coronary reserve substantial These observations support the hypothesis that the acute coronary insufficiency syndrome is caused by reversible coronary ischemic episodes rather than by a new permanent atherosclerotic lesion

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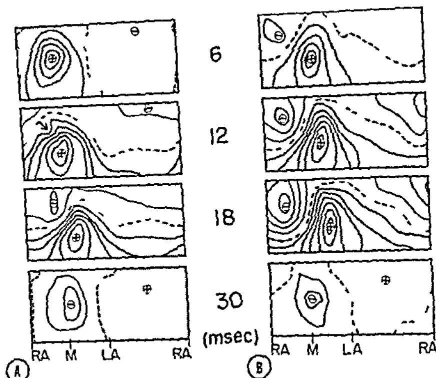


Fig 3 Sequential maps of the case represented in *Fig 2 A* pre infarction maps *B* post infarction maps. Both maps are shown at 6 to 30 msec after the onset of the ventricular depolarization The arrow (pre-infarction map at 12 msec) indicates the pseudopod like irregularity of the equipotential lines

1 The maximum difference in the absolute value of potential from each lead point was below 0 8 mv throughout ventricular activation

2 The voltage difference between pre and post operation was under 25 per cent

3 There was no distinctive difference in the distribution of positive and negative areas and the running of the zero line at either 6 or 30 msec the times at which the greatest differences were observed between pre and post infarction in the infarcted cases

Therefore it may be thought that the operation had no significant effect on the maps

Results

In the early and middle stages of the ventricular depolarization there were consistent common characteristic map patterns such that the negative area occupied the larger part of the right anterior chest surface compared with pre infarction maps However the six cases were divided into two groups (Group A and Group B) according to the map patterns of the late stage Group A (4 cases) consisted of those cases in which the map patterns of the late stage were similar to those of pre infarction while those of Group B (2 cases) were different from those of pre infarction Judging from the epicardial sequence of the ventricular activation process in Group A no intraventricular conduction disturbance occurred but in Group B conduction disturbance probably did occur

A typical case of each group is presented below

Maps of Group A Fig 2 represents a case of a cardiac specimen where a slight sinking and shrinking of the right ventricular free wall corresponds to the infarcted lesion

Fig *3B* illustrates a sequence of maps of this case Pre infarction maps are also shown (Fig *3A*) for easy comparison To illustrate the body surface isopotential map the map was cut and separated along the right mid axillary line on the thoracic surface and was spread open

The shaded area illustrates the positive zone and the white area the negative zone Each solid line illustrates an equipotential line drawn at an interval of 0 4 mv and the broken line illustrates

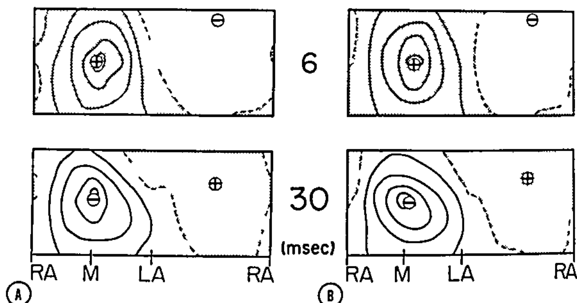


Fig 1 Pre *(A)* and post *(B)* operation maps Both maps are shown at 6 and 30 msec after the onset of the ventricular depolarization The *broken line* indicates the equipotential line of Wilson s central terminal (zero line) The *shaded area* indicates the positive zone where the potential is higher than zero The *white area* indicates the negative zone where the potential is lower than zero (+) indicates a maximum and (−) a minimum *RA* right mid axillary line *M* mid sternal line *LA* left mid axillary line



Fig 2 A cardiac specimen of Group A The shaded area showing slight sinking and shrinking of the right ventricular free wall corresponds to the infarcted lesion

disturbance which might be caused by infarction the pre and post infarction arrival times of the activation at the epicardial surface were obtained from all six cases

The procedure used to measure the arrival time accurately is briefly described below (for a detailed description see reference 6) The direct unipolar and simultaneous bipolar lead electrocardiograms were recorded from 30 to 40 points on the epicardium at speeds of 20 cm/sec through the use of a direct writing electromagnetic oscillograph together with an electrocardiogram using the same time reference

The delineation of the isochronic map expressing the epicardial sequence of the ventricular depolarization of the canine heart was obtained by plotting the points showing the same arrival time of the activation at the epicardial surface

Evaluation for possible artifact induced by surgical open chest operation In order to evaluate whether open chest surgery would introduce artifacts into the map patterns, three dogs were used to determine what differences between before and after the incision of the chest resulted from the surgery itself

The pre and post operation maps taken at 6 and 30 msec are shown in Figs 1A and 1B respectively

The results may be summarized as follows

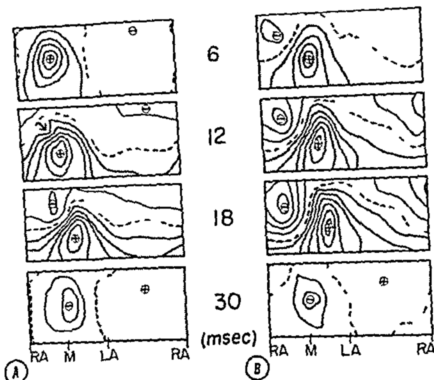


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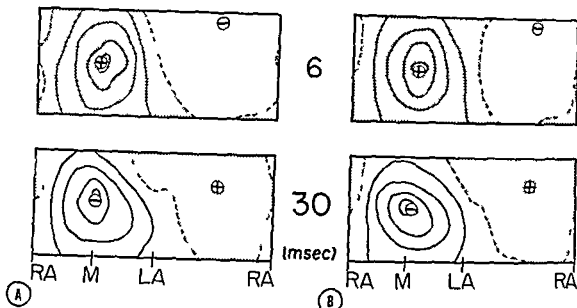


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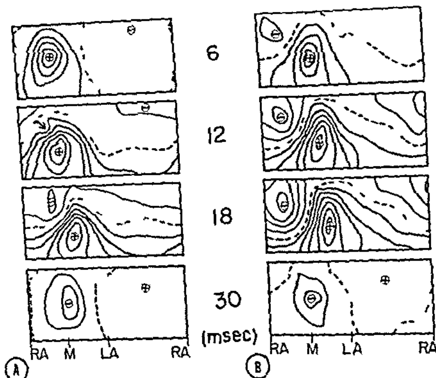


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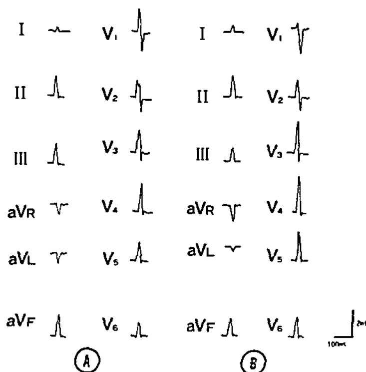


Fig 4 Standard twelve lead ECGs of the case shown in *Fig 2* *A* pre infarction ECG *B* post infarction ECG There are no indications of infarction in the post infarction ECG

the potentials of Wilson's central terminal, which may be called the zero line (+) indicates a maximum and (–) a minimum

In pre infarction maps (Fig 3*A*) at 6 msec from the onset of ventricular depolarization, positive potentials covered nearly the whole anterior chest surface and negative the dorsal surface A maximum was present near the center of the anterior chest surface and a minimum on the upper dorsal

At 12 msec, there appeared a pseudopod like irregularity of the equipotential lines This irregularity might be closely connected with the break through of the electrical wave front to the right ventricular free wall Negative potentials appeared on the right anterior chest surface

At 18 msec, the negative area of the anterior chest surface was more enlarged The minimum moved near the center of the anterior surface The positive area occupied the left anterior and dorsal surface The maximum existed on the left anterior chest surface

At 30 msec, the late stage of ventricular depolarization, the whole anterior chest surface became negative and the dorsal positive The maximum existed on the dorsal and the minimum near the center of the anterior surface

On the other hand, in the maps of post infarction (Fig 3*B*), at 6 msec the negative area occupied a comparatively large part of the right anterior chest surface There also existed a minimum on the right anterior chest surface

At 12 msec the irregularity of equipotential lines could not be observed The negative area of the right anterior chest surface was more enlarged, compared with the corresponding pre infarction map

At 18 msec, the negative area occupied a larger part of the anterior surface, too During 12 to 18 msec the potential of the minimum was lower than that of pre infarction, whereas the potential of the maximum was higher

At 30 msec, the anterior chest surface became negative and the dorsal positive The maximum existed on the dorsal and the minimum near the center of the anterior That is, in this late stage of the ventricular depolarization there was no distinctive difference in map pattern between pre and post infarction

Standard lead ECGs of this case are presented in Fig 4*A* (pre infarction) and in Fig 4*B* (post infarction)

In comparing Fig 4*B* with Fig 4*A*, a diminished R wave in Lead V_1 and increased R waves in Leads V_3 and V_4 were observed, but no abnormal Q waves could be recognized

As mentioned above to diagnose right ventricular infarction through the maps the distribution of the negative area and the location of the minimum are very important Therefore, to demonstrate the mean distribution of the negative and positive area of all four cases, the average maps[5] are presented in both pre infarction (Fig 5*A*) and post infarction (Fig 5*B*) from 6 to 30 msec of the ventricular depolarization The distributions of the negative and positive areas of both average maps were made on the basis of the mean algebraic sum of the potential obtained from the respective lead points on the canine surface in both pre and post infarction at 1 5 msec intervals The minimum and maximum of each case is also shown (In case of multiple minima or maxima appearing only the primary minimum or maximum is shown in each map)

Consistent features of the right ventricular infarction inferred from the individual maps and average maps were as follows

1 In the early stage of the ventricular depolarization the negative area occupied a comparatively large part of the right anterior chest surface and in the middle stage the larger part of the

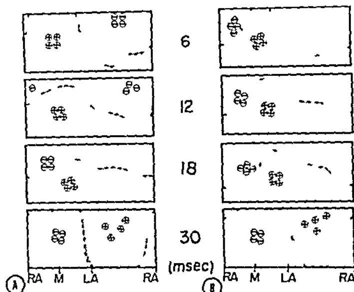


Fig 5 These maps show Group A s mean distribution of positive and negative areas at 6 to 30 msec after the onset of the ventricular depolarization The maximum and minimum of each case in Group A are also shown *A* pre infarction average maps *B* post infarction average maps



Fig 6 A cardiac specimen of Group B The area showing slight sinking and shrinking of the right ventricular free wall corresponds to the infarcted lesion

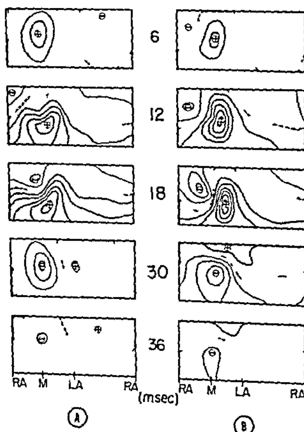


Fig 7 Sequential maps of the case represented in *Fig 6* *A* pre infarction maps *B* post infarction maps Both maps are shown at 6 to 36 msec after the onset of the ventricular depolarization

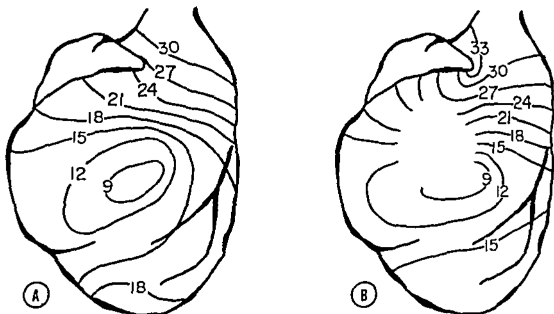


Fig 8 Schematic illustration of the epicardial activation process *A* epicardial isochronic map of the pre infarction *B* isochronic map of the post infarction The figure indicates the time (msec) after the onset of the ventricular depolarization

right anterior surface was also occupied by the negative area

2 A minimum appeared on the right anterior chest surface in the earlier stage

Maps of group B In the late stage of the ventricular depolarization, two cases of infarction differed from the other four cases in map pattern One cardiac specimen of these two cases is repre sented in Fig 6 (the slightly sinking and shrinking palish region is the infarcted lesion) Fig *7B* illustrates the sequential maps of this case Fig *7A* shows those of pre infarction for easy compar ison

This case also shows common characteristic map patterns of right ventricular infarction in the early and middle stages (note the distribution of the negative area and location of the minimum) However in the late stage (30 and 36 msec) a positive area and a maximum appeared on the upper anterior chest surface This map pattern was different from that of pre infarction or that of the other four cases in which the whole anterior surface was occupied by the negative and the maximum existed on the dorsal surface

The post infarction epicardial isochronic map of this case is shown in Fig *8B* and pre infarction map is illustrated in Fig *8A* Isochronic lines were drawn every 3 msec and the shaded area (Fig *8B*) indicates the infarcted lesion

A comparison of Figs *8A* and *8B* suggests that there might be some delay of the epicardial excitation in the upper area ajacent to the infarcted lesion since the isochronic lines of 24 27 30 and 33 msec showed gathering toward the infarcted lesion

The standard twelve lead ECGs of this case are shown in Fig *9A* (pre infarction) and Fig *9B* (post infarction) There were no abnormal Q waves in any lead although a diminished R wave was observed in Lead V_1 The QRS configuration of Leads aV, and aV were different between pre and post infarction However no notch or slur was recognized in any lead though the QRS duration of post infarction was slightly longer than that of pre infarction

Discussion

Body surface isopotential maps have several advantages compared with conventional electrocardiograms Among the important advantages are that unlike the twelve lead ECG and vector cardiogram maps give significant information from the right anterior chest surface and dorsal region Another advantage is that maps represent the ventricular activation process well

Using these advantages of maps many investigations have been done For example Blumenschein and associates reported that various types of right ventricular hypertrophy can be differentiated according to underlying disease by maps Sugenoya and colleagues[1] and Niimi[16] demonstrated that in right bundle branch block the degree or site of the right bundle block can be well diagnosed by maps

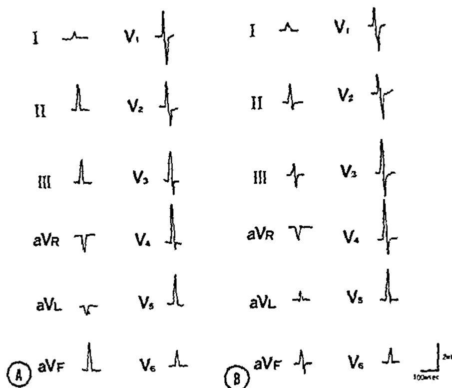


Fig 9 Standard twelve lead ECGs of the case shown in Fig 6 A pre infarction ECG B post infarction ECG There is no notch or slur in the post infarction ECG

The intent of this experiment was to investigate the feasiblity of diagnosing right ventricular infarction through the use of maps which have significant information of cardiac electrical events that might be projected to the right anterior chest surface

Right ventricular infarction The most characteristic feature of maps of right ventricular infarction is that in the early stage of the ventricular depolarization the negative area occupied the right anterior chest and the minimum also appeared there Since pre and post infarction measurements in this study were taken from the same dogs intramural electrical events could not be measured because of technical limitations The implantation of detecting leads in the cardiac wall is itself an invasive technique and may have generated spurious disturbances in addition to those being measured However given studies done previously on the ventricular activation process in dogs and the electrical information obtained from the epicardial surface the change in map pattern caused by right ventricular infarction can be explained as follows

In pre infarction maps at 6 msec after the onset of ventricular depolarization the activation front mainly spreads ventrally from the ventricular septum and also spreads outward from the left and right cavity toward the left and right anterior free walls Therefore in the map the positive area covers nearly the whole anterior chest and the negative area covers the dorsal region A maximum is present near the central position of the anterior chest surface and a minimum on the dorsal As ventricular activation proceeds there occurs a breakthrough of the electrical wave front to the epicardium of the right ventricular free wall When the area where the wave front has reached the epicardium is small enough there appears a potential sink in the positive area (pseudopod like irregularities of equipotential lines) And as the area becomes larger the negative area appears on the right anterior chest and enlarges as ventricular activation proceeds

In maps of right ventricular infarction there is no electrical activity in the infarcted lesion The wave front which spreads from the right cavity toward the right free wall is impaired by infarction Because of this lack of the electromotive

force which would otherwise have proceeded to the right anterior wall, the negative area and minimum appear on the right anterior chest in the map in the early stage

In the middle stage, two negative areas, one resulting from wave fronts having reached the epicardium and the other caused by infarction, merge so that a larger part of the anterior chest than in the pre infarction map is occupied by a negative area As the diminished wave front, which spreads to the right, cannot cancel out the wave front which spreads from the left cavity to the left free wall completely, the potential of the maximum located on the left anterior chest is larger than that of pre infarction In the late stage so long as no conduction disturbance occurs the larger part of the right ventricular wall has depolarized with little difference in both pre and post infarction Therefore, maps of post infarction resemble those of pre infarction in Group A

The diminished R wave of Lead V_1 is recorded in a standard twelve lead electrocardiogram but there are no Q waves observed in any lead Thus, it is very difficult to diagnose with confidence right ventricular infarction unless data of pre and post infarction ECGs can be acquired However through the use of maps, right ventricular infarction can be diagnosed easily by noting the negative area and minimum on the right anterior chest in the early stage

Conduction disturbance In the case of the canine heart, the conus pulmonaris of the right ventricle and the basal region of the left ventricle are very late to excite As the electrical wave front arising from the conus pulmonaris is not so large as that arising from the larger mass of the basal region of the left ventricle in the late stage in the maps reflecting this main wave front the positive area occupies the whole dorsal region and the negative the anterior However if any conduction disturbance occurs the map pattern will change In the representative case (Fig *7B*), conduction disturbance occurs in the upper region adjacent to the infarcted lesion Therefore it is thought that the upper part of the right ventricle depolarizes after the basal region has depolarized Reflecting this conduction delay, the positive area and minimum appear on the upper anterior chest in the map

A body surface isopotential map based on many lead points on the surface including the upper anterior region is indispensable for easier and more accurate diagnosis of the conduction disturbance caused by infarction

Summary

This investigation was designed to diagnose right ventricular infarction, which is difficult to diagnose by the standard twelve lead ECG through the use of body surface isopotential maps which have significant diagnostic information

Right ventricular infarction was experimentally caused by ligation of the canine right coronary artery Each dog had a series of maps recorded before and a week after experimentally induced myocardial infarction

The common features of maps in right ventricular infarction are

1 In the early stage of the ventricular depolarization the negative area occupies a comparatively large part of the right anterior chest surface, and in the middle stage, the larger part of the right anterior surface is also occupied by the negative area

2 A minimum appears on the right anterior chest surface in the early stage

The delayed excitation resulting from intraventricular conduction disturbance caused by infarction as verified by the epicardial isochronic map is also well represented by the body surface isopotential map

In conclusion, through the use of body surface isopotential maps it is much easier to diagnose right ventricular infarction and intraventricular conduction disturbance caused by infarction even in cases in which the standard twelve lead ECG does not show the abnormalities clearly

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Influence of nonsteroidal anti-inflammatory drugs on ouabain toxicity

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Several prostaglandins have been reported to be effective in preventing or terminating experimentally induced cardiac arrhythmias Prostaglandin E_1 has been shown to suppress arrhythmias resulting from thialbarbitone anesthesia and myocardial ischemia in dogs [1] barium chloride induced arrhythmias in rabbits,[2] and ouabain induced arrhythmias in cats [2] In addition, this acidic lipid significantly increased the toxic dose of ouabain when given prior to the administration of the glycoside [3]

Similarly prostaglandin E was effective in terminating arrhythmias resulting from myocardial ischemia and cardiac glycoside toxicity in the pig and dog[4] while prostaglandin F_{α} was reported to be effective in reversing a wide range of experimental arrhythmias [5, 6] and is the only prostaglandin that has been employed clinically in the treatment of cardiac arrhythmias In this regard Mann reported therapeutic effects in five of six patients exhibiting constant extrasystoles and in one patient with a partial A V block produced by digitalis However the results obtained in patients with acute tachyarrhythmias were not convincing

Although the mechanism of the antiarrhythmic action of the prostaglandins is unclear at least two possible mechanisms have been suggested Kelliher and Glenn[7] suggested that these acidic lipids may be effective in digitalis toxicity as a result of their ability to modulate the release of norepinephrine from sympathetic neurons[8, 9] thus reducing the neural component of the arrythmogenic action of these glycosides [10, 11] On the other hand Forster and associates[4] concluded that the major antiarrhythmic action of the prostaglandins may be related to their ability to increase sinus rate and improve conduction thus allowing transition to a sinus rhythm without any effect on ventricular pacemakers

The purpose of this study was to investigate the relationship between endogenous prostaglandins and the sympathetic nervous system during cardiac glycoside toxicity To this end we studied the toxicity of ouabain in animals with a normal capacity to synthesize prostaglandins and in animals pretreated with nonsteroidal anti inflammatory drugs (NSAID) known to inhibit endogenous prostaglandin synthesis [12]

Methods

Preparation of experimental animals Thirty nine dogs of either sex weighing 7 to 15 kilograms were anesthetized with pentobarbital sodium 30 mg /Kg intravenously Catheters were placed in a femoral artery and attached to a Statham pressure transducer for the measurement of arterial blood pressure and in a femoral vein for drug injection A standard Lead II electrocardiogram (ECG) was monitored in all animals for pacemaker site approximation and heart rate was derived from the ECG via a Beckman cardiotachometer All parameters were recorded on a Beckman R 411 Dynograph and the ECG was continuously monitored on a Tektronix oscilloscope

Animals were allowed to stabilize 30 minutes after surgery At the beginning of this stabiliza

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tion period a supplemental dose of pentobarbital was administered so as to obviate the need for additional anesthetic during the experimental procedure Animals were allowed to breathe room air spontaneously throughout each experiment and were maintained at 37° C through the use of a K Aquatic pad Body temperature was monitored via a rectal termistor and a telethermometer (Yellow Springs) Arterial blood pO pCO and pH were determined periodically during each experiment and were found to remain within normal limits throughout all experiments

Ouabain infusion In all experiments ouabain (Sigma Chemical Co) dissolved in normal saline was infused intravenously using a Harvard infusion pump at a rate of 2 µg/Kg /min Ouabain solutions were made fresh daily in suitable concentrations to allow for delivery of the proper dose with an infusion rate not exceeding 0 1 ml / min During the infusion the dose of ouabain necessary to produce premature ventricular beats (PVB) ventricular tachycardia (VT) and ventricular fibrillation (VF) were recorded Ouabain infusion was continued until death in all experiments

Nonsteroidal anti inflammatory drug pretreatment In experiments requiring pretreatment with a nonsteroidal anti inflammatory drug the agent used was dissolved in normal saline by adjusting the pH of the saline into the alkaline region to facilitate dissolution of these acidic drugs All solutions were made fresh daily Aspirin (Sigma Chemical Co) ibuprofen (Motrin Upjohn) and AF29590 (Abbott) were dissolved in saline by carefully titrating with 0 1 N NaOH while indomethacin (Indocin Merck Sharpe and Dohme) was dissolved by careful titration with 0 1 N Na CO In each case the particular dose of the drug was dissolved in 3 to 5 ml of alkaline saline and diluted to approximately 10 ml prior to administration The pH of the final solutions was in the range of 6 8 to 7 2 All NSAID were infused intravenously over a period 3 to 5 minutes In pretreatment experiments ouabain infusion was not begun until 25 to 30 minutes after administration of the NSAID thus allowing adequate time for the prostaglandin synthetase inhibitory action of aspirin indomethacin or ibuprofen to become effective As in the non treated group ouabain was infused at a rate of 2 µg/Kg /min until death noting the dose of ouabain necessary to produce PVB VT and VF The influence of these agents on ouabain toxicity was determined by comparing the doses of ouabain required to produce each arrhythmia in control animals to that necessary in animals pretreated with each NSAID using Student s t test for unpaired data (Monroe 1930 calculator)

Sympathetic neuron blockage Another group of animals was pretreated with guanethidine prior to treatment with saline or a NSAID The animals were prepared in the same manner as those in the first group except that in addition snares were placed around both carotid arteries in the cervical region so that a bilateral carotid occlusion reflex could be elicited by gently elevating the snares Guanethidine pretreatment was begun 24 hours prior to surgical preparation of the animals at this time guanethidine (10 mg / Kg) was administered intramuscularly An additional dose of 3 mg /Kg was administered intramuscularly immediately after the animals were anesthetized on the day of the experiment Criteria for guanethidine inhibition of sympathetic activity were the absence of an elevation of blood pressure or heart rate upon bilateral carotid occlusion If these criteria were met animals were administered saline aspirin (50 mg /Kg) or indomethacin (3 mg /Kg) prior to the infusion of ouabain As in the other experiments the doses of ouabain necessary to produce PVB VT and death were recorded The influence of NSAID on ouabain toxicity in these animals was evaluated by comparing the dose of ouabain at each end point in animals receiving ouabain alone to the dose of ouabain in animals pretreated with aspirin or indomethacin using Student s t test for unpaired data

Results

Influence of NSAID on ouabain induced arrhythmias The effects of indomethacin 3 mg / Kg aspirin 50 mg /Kg ibuprofen 5 mg /Kg and AR29590 10 mg /Kg on the dose of ouabain required to produce the onset of premature ventricular beats (PVB) are summarized in Table I The first three of these anti inflammatory drugs are prostaglandin synthetase inhibitors[11] whereas AR29590 has not been found to inhibit this enzyme[1] In control experiments an 88 ± 4 µg/Kg dose of ouabain was required to produce this early arrhythmia in ten control dogs Clearly all of the nonsteroidal anti inflammatory agents employed except AR29590 significantly reduced

Table I Influence of NSAID on ouabain toxicity

Drug and number of animals	Ouabain dose (μg/Kg) required to produce arrhythmias*		
	Premature ventricular beats	Ventricular tachycardia	Ventricular fibrillation
Ouabain only (6)	88 ± 4	116 ± 5	143 ± 25
Ouabain + indomethacin (3 mg/Kg) (6)	62 ± 11†	80 ± 10†	112 ± 9†
Ouabain + aspirin (50 mg/Kg) (6)	76 ± 4†	98 ± 5†	127 ± 9†
Ouabain + ibuprofen (5 mg/Kg) (6)	61 ± 9†	92 ± 8†	113 ± 10†
Ouabain + AR29590 (10 mg/Kg) (6)	81 ± 6	106 ± 10	136 ± 11

All values are mean ± 1 standard error of the mean for the number of experiments shown in parentheses
†Indicates significant difference ($p < 0.05$) from ouabain above

the total dose of ouabain required to produce PVB The dose of ouabain required to produce premature ventricular beats in animals pretreated with indomethacin, aspirin and ibuprofen was 62 ± 11, 76 ± 4, and 61 ± 9 μg/Kg, respectively AR29590 reduced the ouabain dose to 81 ± 6 μg/Kg but this decrement in ouabain dose was not statistically significant

Indomethacin, aspirin, and ibuprofen pretreatment significantly reduced the dose of ouabain required to produce VT (Table I) Control animals treated with ouabain alone developed ventricular tachycardia at a dose of 116 ± 5 μg/Kg while animals pretreated with indomethacin required only 80 ± 10 μg/Kg to reach this endpoint Similarly animals pretreated with aspirin and ibuprofen developed ventricular tachycardia at dose of 98 ± 5 μg/Kg and 92 ± 8 μg/Kg of ouabain respectively As was the case with the PVB endpoint AR29590 slightly reduced the ouabain dose in this case to 106 ± 10 μg/Kg but the reduction was not significant

The influence of these nonsteroidal anti inflammatory drugs on the lethal dose of ouabain is also shown in Table I In ten control dogs 143 ± 2 5 μg/Kg of ouabain was required to produce ventricular fibrillation but in animals pretreated with indomethacin aspirin and ibuprofen the lethal dose of ouabain was significantly reduced to 112 ± 9 127 ± 9, and 113 ± 10 μg/Kg respectively The reduction in the lethal dose of ouabain (136 ± 11 μg/Kg) in animals treated with AR29590 was not significant All animals died in ventricular fibrillation

Influence of NSAID and ouabain on blood pressure and heart rate All nonsteroidal anti inflammatory drugs produced a slight but insignificant increase in arterial blood pressure Ouabain infusion produced a significant rise in blood pressure in all experiments There were no significant differences in the blood pressure response to ouabain infusion in NSAID pretreated and non pretreated dogs

The effects of the NSAID employed in this study on heart rate were unimpressive In most instances heart rate was slightly but not significantly, elevated after treatment with indomethacin aspirin ibuprofen or AR29590 In addition it was also noted that there was no significant difference in the rate of the ventricular tachycardia developed as a result of ouabain administration in unpretreated (214 ± 8 beats/min) and indomethacin (221 ± 8 beats/min) aspirin (210 ± 6 beats/min) ibuprofen (213 ± 9 beats/min) or AR29590 (209 ± 7 beats/min) treated animals

Influence of adrenergic neuronal blockade on NSAID action In order to determine the possible involvement of the sympathetic nervous system in the action of these nonsteroidal anti inflammatory drugs three groups of dogs were pretreated with guanethidine All the guanethidine pretreated animals exhibited a lack of blood pressure and heart rate responses during bilateral carotid occlusion and this was considered adequate evidence for sympathetic neuronal blockade Five guanethidine treated animals were infused with ouabain 2 μg/Kg/min after pretreatment with saline while six animals were pretreated with aspirin 50 mg/Kg and three animals with indomethacin 3 mg/Kg thirty minutes prior to initiating ouabain infusion Fig 1 summarizes the effects of guanethidine pretreatment on the ability of aspirin and indomethacin to enhance the toxicity of ouabain Neither aspirin nor indomethacin significantly altered the dose of

ouabain required to reach any level of toxicity in the presence of sympathetic neuronal blockade Ouabain produced premature ventricular beats ventricular tachycardia and death at doses of 96 ± 8 118 ± 4 and 115 ± 11 μg/Kg respectively in saline pretreated animals After pretreatment with 50 μg/Kg of aspirin the dose of ouabain required to reach each of these endpoints was 95 ± 10 110 ± 10 and 114 ± 5 μg/Kg respectively Similarly after indomethacin administration to guanethidine pretreated animals 90 ± 8 μg/Kg of ouabain was required to produce premature ventricular beats 124 ± 7 μg/Kg to produce ventricular tachycardia and 158 ± 5 μg/Kg to produce death Thus neither NSAID significantly enhanced ouabain toxicity in the presence of guanethidine Furthermore all of the animals treated with guanethidine died in cardiac arrest rather than ventricular fibrillation

Discussion

The results of this study clearly demonstrate that aspirin indomethacin and ibuprofen enhance the cardiac toxicity of ouabain Presumably this action is related to the ability of these agents to inhibit prostaglandin synthetase an enzyme system required for the synthesis of endogenous prostaglandins from phospholipid precursors [1 5] although we can not rule out contributions of other actions of these drugs [3] Evidence for our contention that inhibition of prostaglandin synthesis is indeed responsible for this enhancement of ouabain toxicity is based on the finding that AR29590 a nonsteroidal antiinflammatory drug which does not inhibit prostaglandin syntheta e [4] did not significantly alter ouabain toxicity

Furthermore results of this study appear to relate depressed prostaglandin synthesis and elevated sympathetic nervous system activity to the increased ouabain toxicity after NSAID treatment If one assumes that the major action of guanethidine is to inhibit sympathetic neuron activity the fact that guanethidine prevented the action of aspirin and indomethacin to enhance ouabain toxicity is evidence for the importance of a neural component in their action on cardiac glycoside induced arrhythmias In this regard previous studies have shown that prostaglandin synthetase inhibition augments norepinephrine release upon stimulation of sympathetic nerves [1]

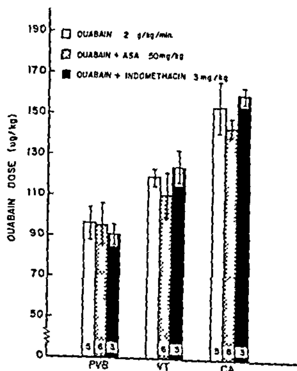


Fig 1 This figure illustrates the effect of sympathetic neuronal blockade by guanethidine on the interaction of NSAID and ouabain *Open bars* represent the mean dose of ouabain ± 1 standard error required to produce premature ventricular beats (*PVB*) ventricular tachycardia (*VT*) and death by cardiac arrest (*CA*) in animals pretreated only with guanethidine *Cross hatched* and *solid bars* represent the mean ouabain dose ± 1 standard error required to produce these same arrhythmias in animals with sympathetic neuronal blockade which were pretreated with aspirin and indomethacin respectively The number at the bottom of each bar indicates the number of experiments

At present there are two widely divergent schools of thought with respect to the importance of cardiac sympathetic activity in digitalis toxicity One school of thought holds that myocardial norepinephrine plays no role in the electrical or mechanical actions of cardiac glycosides on the heart [1] while the other suggests that there is a causal relationship between digitalis induced sympathetic nerve excitation and the development of cardiac rhythm disturbances [9 21] Regardless of the importance of a direct neural action of digitalis to its arrhythmogenic action it is clear that cardiac norepinephrine whether released directly by the glycoside or released as a

result of normal sympathetic tone, would have at least an additive action to that of digitalis on cardiac electrophysiological events [2] Thus, an intervention such as prostaglandin synthetase inhibition which acts to increase the circulating level of norepinephrine as well the quantity released in the heart as a result of normal or elevated sympathetic tone would reduce the dose of cardiac glycoside required to elicit cardiac toxicity

The experiments involving animals pretreated with guanethidine do not support or reject a neural component of ouabain toxicity Although guanethidine pretreatment did not significantly increase the dose of ouabain required to reach any of the three endpoints this agent did not decrease heart rate as much as in other studies which have reported a protective action of this agent against ouabain toxicity [1] In the pentobarbital anesthetized dogs employed in this study heart rates in our control group were 154 ± 8 beats per minute whereas, in animals pretreated with guanethidine it was 128 ± 9 Raines and colleagues, [3] in reporting a protective effect of guanethidine in dial urethane anesthetized cats reported a fall in rate of over 30 per cent after pretreatment with a larger dose of guanethidine The lack of a protective effect of guanethidine in this study may be the result of lower sympathetic tone during pentobarbital anesthesia as compared to the tone achieved with dial urethane In this regard Stickney [4] demonstrated that ouabain cardiotoxicity is developed at a lower dose in chloralose urethane anesthetized cats than in pentobarbital anesthetized cats, and suggested that this difference may be the result of lower sympathetic tone in pentobarbital anesthetized animals This is in agreement with previous reports that a reduction in heart rate reduces the arrhythmogenic effects of digitalis [25]

The demonstration of enhanced digitalis toxicity during simultaneous administration of nonsteroidal anti inflammatory drugs such as aspirin indomethacin, and ibuprofen would seem to be of important clinical significance given the large number of patients taking cardiac glycosides and the ever increasing use of nonsteroidal anti inflammatory drugs If one considers the normally low therapeutic index of the cardiac glycosides, any intervention that would tend to reduce this factor further might be expected to compound the already serious problem of digitalis toxicity

Summary

The effect of nonsteroidal anti inflammatory drugs (NSAID) on the toxicity of ouabain was studied in pentobarbital anesthetized dogs. Two types of NSAID were employed (1) the prosta glandin synthetase inhibitors aspirin indometha cin and ibuprofen, and (2) AR29590 a NSAID reported to be devoid of prostaglandin synthetase inhibitory activity Pretreatment with aspirin 50 mg /Kg , indomethacin, 3 mg /Kg and ibuprofen 5 mg /Kg significantly reduced the doses of ouabain required to produce onset premature ventricular beats (PVB) ventricular tachycardi (VT), and ventricular fibrillation (VF) wher compared to animals pretreated only with saline The dose of ouabain required to produce each o these arrhythmias in animals pretreated wit AR29590 10 mg /Kg was not significantl different from saline pretreated animals The rol of the sympathetic nervous system in th enhanced toxicity of ouabain after NSAI administration was studied in dogs durin adrenergic neuronal blockade produced by guane thidine In guanethidine pretreated dogs the were no significant differences in the doses ouabain required to produce PVB, VT, or deat between aspirin and indomethacin and salir treated dogs The results of this study suggest protective action of endogenous prostaglandins cardiac glycoside toxicity since inhibition of pro taglandin synthesis resulted in enhanced toxicit Furthermore this enhancement of ouabain toxi ity appears to be the result of increased cardi adrenergic influences since it is prevented guanethidine treatment

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Clofibrate effects Mitochondria vs exercise tolerance in aging hamsters

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Mitochondria the ultrastructural elements of cells involved in oxidative phosphorylation have recently been examined in myocardium in animals and man for evidence of ischemia and autolysis[1] In a comparison of mitochondria from several different tissues in young and old hamsters Inamdar and colleagues[3] found that mitochondria from aged animals were less stable and more fragile The differences between young and old were particularly striking for muscle both skeletal and cardiac compared to liver At one month of age, the yield of mitochondrial protein expressed as mg /Gm tissue was 6 4 for skeletal muscle, 21 6 for myocardium and 17 9 for liver By 13 months of age (comparable to about 50 years in the human) the yield was 1 7 for skeletal muscle, 10 8 for myocardium, and 13 3 for liver The cause of this reduction appeared to be increased fragility of the mitochondria from aging animals

It was therefore of considerable interest when Inamdar Person and Mackler[4] found that chronic administration of clofibrate (Atromid S) to hamsters increased the yield of mitochondria from skeletal muscle of aging hamsters by 64 per cent and from myocardium by 39 per cent Since clofibrate is used in the treatment or prevention of atherosclerosis due to hyperlipidemia the exciting possibility occurred to us that the mitochondrial 'rejuvenation' might indicate a more protean effect of this drug Whereas the initial trial had extended for only one month we decided to try a longer course and to examine for any improvement in exercise tolerance in these aging hamsters Hamsters are ideal as an animal model for aging studies since they have a maximum life expectancy of two years and are well defined genetically

In a preliminary experiment, we tried swimming duration as a quantitative expression of physical fitness Since the hamster s hair and cheek pouches are capable of trapping air, we found that they could float with very little energy expenditure We therefore used a graded treadmill test for work performance

Materials and methods

Twelve hamsters born 15 months prior to the commencement of our experiments were obtained from the Lakeview Hamstery Lakeview New Jersey Control animals were fed Purina Rat Chow and water *ad libitum* The experimental animals were fed the same diet with clofibrate added 0 5 per cent by weight

A Quinton small animal treadmill* was used for testing exercise capacity as described previously for rats by Wranne and Woodson[5] This mill permits exercising up to 10 animal simultaneously at speeds up to 54 meters per minute and inclinations up to 27 degrees An

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*Model 4? 15 Quinton Instrument Co Seattle Wa h

Table I Hamster running time (in minutes)

	Control (Animal no)						*Treated with 0 5% clofibrate (Animal no)*						*Group averages*	
Date	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*Control*	*Treated*
4 8-75	15 90	20 43	15 90	16.49	19 67	19 35	17 47	19 75	12.90	19 75	19 75	15 30	18 0	17 5
4 29 75	14 0	20 87	17 80	14 00	19 62	19 62	15 00	19 13	12 99	21 70	21 70	16 37	17 0	18 0
4 30-75	15 16	19 00	14 00	Died	20 00	20 00	13 10	17 50	14 80	20 49	20 20	17 60	18 0	17 0
Start of clofibrate														
5 1 75	17 70	22.14	12 70		21 36	18 80	15 30	18 99	15 40	21 41	21 70	19 76	18 0	19 0
5 2 75	15 98	22 03	14 48		19 50	19 50	13 30	18 90	17 80	20 00	23.00	22.63	18 0	19 0
5 5-75	17 65	25 00	15 50		20 00	16 40	13.25	19 60	16 33	18 54	21 76	24 68	19 0	19 0
5-9-75	17 10	21.94	14 14		20 10	19 60	11 54	20 87	15 13	18 0	19 73	20 15	19 0	18 0
5-12 5	16 6	21 70	13 00		21 90	21 90	11 20	22.70	15 20	18 90	21 80	20 14	19 0	18 5
5-16- 5	17 30	23 69	12 63		19 45	17 55	Died	22 35	15 87	18 50	21.56	22.35	18 0	20 0
5-19-75	16 39	21 70	17 76		21 40	17 13		22 27	17 06	19 75	21 30	13 84	19 0	19 0
5-23- 5	17 80	22 90	17 80		22 00	14 50		20 50	16 63	17 30	20 50	20 50	20 0	19 0
5 27 75	17 90	2 00	13 95		18 50	18 50		19 72	15 30	17 80	18 72	21 22	18 0	19 0
5 30-75	17 00	3 00	18 54		21 03	17 40		20 40	13 46	20 00	20 30	20 00	19 0	19 0
6-2 5	18 00	21 54	17 33		18 70	18 90		21 65	12 60	20 76	18 00	14 32	19 0	17 0
6-6-75	20 72	20 16	18 00		21 60	17 58		20 35	12.30	19 31	18 43	16 79	20 0	17 0
6-9 75	13 20	20 45	16 79		27 60	20 90		20 10	12 96	20 10	16 44	15 91	19 0	17.0
6-13-75	19 00	20 72	16 90		18 59	18 96		23 00	16 63	20 00	13 10	19 89	19 0	19 0
6-16- 5	18 48	19 81	17 30		18.45	19 00		21 50	14 78	21 00	17.85	19 15	19 0	19 0
6-20-75	19 00	20 15	19 00		18 45	21.00		18 00	15 00	21 00	20 00	18 00	20 0	18 0
6-23-75	19 81	17 5	18 00		21 30	19 7		21 30	10 50	20 86	17 50	13 00	19 0	17 0
6-27 5	19 27	17 20	17 80		17 80	18 41		19 35	19 00	19 35	18 50	18 99	18 0	19 0
8-19-75	24 30	15 63	16 14		20 63	17 12		23 32	8 30	21 81	21.81	Died	19 0	19 0

electrically charged grid at the downhill end of the treadmill provides motivation for maximum work Initially the speed of the treadmill was 19 M/min (7 mph) at an inclination of 12 5 degrees The inclination was increased step wise by 2.5 degrees every three minutes to a maximum inclination of 27 degrees and then the speed was increased by 2 7 M/min (0 1 mph) at three minute intervals The maximum time for running was recorded for each animal The end point of the test was taken as that time when the hamster spent more than five seconds resting on the electrically charged grid Each animal was run twice a week for two months and again at 3.5 months from the start of the drug

Results

In the course of four treadmill runs prior to drug treatment of half of the hamsters one of the animals designated as a control died One treated hamster died in the third week of treatment and one died just prior to the last run at 3 5 months Obviously the treatment *did not* improve surviv al although he numbers are too small for any confidence in the differences

The individual and average duration of tread mill runs are given in Table I In the period before *treatment* there is no significant difference between the exercise capacity of the two groups of animals using the Wilcoxon signed rank test (p value > 2) Following administration of the clofi brate each animal was run 18 times on the treadmill over a period of 56 days and finally at 3 5 months The treated group on the average ran three per cent less time than the control group an insignificant difference Using the Wilcoxon signed rank test there is no difference due to treatment with clofibrate (p = 2)

Discussion

The exciting promise of clofibrate the ability to rejuvenate mitochondria in muscle was not fulfilled for exercise tolerance The search for a pharmacologic fountain of youth will undoubt edly go on but there may be a useful message here The correlation is not perfect between func tion measured *in vivo* and *in vitro* The mech anisms of disease states and of acute pathophysi ology should continue to be pursued with a variety of disciplines including ultrastructural

and metabolic studies, but extrapolations, as always should be restrained

Summary

Mitochondria in skeletal and cardiac muscle have been found to be less stable in aging hamsters in contrast to preparations from young animals We have found previously that clofibrate (Atromid S) will reverse this degeneration in the older hamsters This study examined the exercise tolerance of aged hamsters to see if clofibrate had a parallel effect on exercise tolerance as had been shown for muscle mitochondria stability Maximal duration of exercise for hamsters on a treadmill was measured in a control and treatment group before and after treatment with clofibrate There was no improvement in exercise tolerance with clofibrate We conclude that inferences of functional effects in intact animals from changes found in isolated tissue preparations should be drawn with caution

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Post exercise thallium 201 myocardial scanning: A clinical appraisal

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Rapid progress has been made in radionuclide scanning of the myocardium. The choice of isotopes and imaging systems allows practical application of scanning in the diagnosis of coronary artery disease, myocardial infarction, and in the evaluation of aortocoronary bypass graft status. Whereas the limitations of the conventional diagnostic techniques of angiography and exercise electrocardiography have been defined in recent years, the advantages and disadvantages of myocardial scanning in the clinical setting are just beginning to be appreciated.

To assess the value of myocardial scanning, we evaluated 42 consecutive stress and resting myocardial scans using thallium 201 (Tl 201) and a new mobile gamma camera in 38 patients with suspected or documented coronary disease. Among these were 17 patients with aortocoronary bypass grafts. The results of these scans were compared with treadmill exercise electrocardiograms and with coronary and ventricular cineangiography.

Methods

The patients were considered in four groups. *Group I* had 15 patients with severe coronary artery disease, defined as coronary luminal obstruction on angiogram greater than 75 per cent of the coronary diameter in at least *one* major coronary artery. *Group II* had four patients with mild coronary disease, defined as luminal obstruction less than 50 per cent of the coronary diameter in one or more major coronary arteries. *Group III* had three patients with angiographically normal coronary arteries and left ventricular contraction patterns. *Group IV had 17 patients* who had undergone aortocoronary bypass surgery. Three patients initially in Group I had subsequent aortocoronary bypass surgery and were restudied; these patients are also included in Group IV. Two additional patients had treadmill tests and Tl 201 scans but no angiography and were not included in the above groups.

Treadmill testing. Patients were exercised to either 90 per cent of their age predicted maximal *heart* rate, or to the onset of angina, severe fatigue, or significant ST segment or rhythm changes using the Bruce *protocol*. Tl 201 was injected intravenously 30 to 45 seconds after reaching maximal exercise levels through a 19 gauge scalp vein needle placed in an antecubital vein prior to exercise. The bolus of Tl 201 was flushed with 10 c.c. saline and a fast saline drip.

Treadmill tests were considered *positive* in the presence of at least 1 mm. J junctional depression with flat or downsloping ST segments. They were considered *nondiagnostic* if (a) ST segment changes occurred at an adequate heart rate but failed to meet the specific criteria of a positive test, (b) ST segment changes suggesting a positive test occurred in the presence of abnormal baseline ST segments, when ST changes occurred with pre test hyperventilation, in the presence of elec

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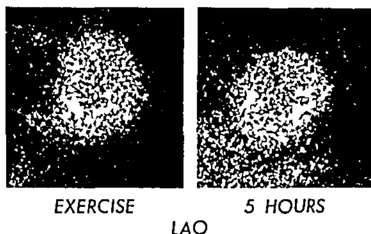


Fig 1 Normal exercise scan (*left*) and rest-redistribution (*right*) Note the increased hepatic activity at rest In this and all subsequent figures left anterior oblique views are shown

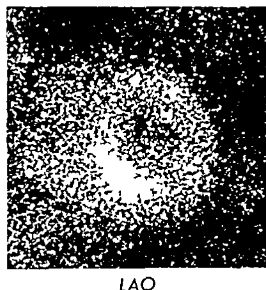


Fig 2 A positive exercise myocardial scan in a patient with single vessel severe coronary disease A discrete defect is shown at the lower right in the 5 o clock position

trocardiographic criteria for left ventricular hypertrophy or intraventricular conduction defects or in patients receiving medications known to affect ST segments such as digitalis, or (c) an adequate heart rate in the absence of diagnostic ST changes, could not be attained Treadmill tests were interpreted as *negative* if ST segments were normal at an achieved heart rate of 90 per cent of the age predicted maximum

Myocardial scanning At the point of maximal treadmill exercise 2 mCi Tl 201 were injected intravenously Imaging was begun within six minutes with the patient in the supine position, using an Ohio Nuclear Series 120 mobile scintillation camera Anterior 60 degree left anterior oblique and left lateral views were obtained, and required an average of four minutes per view for 200 000 counts The presence of one or more defects reflecting regions of reduced myocardial uptake of Tl 201 constituted a positive scan Resting myocardial scans were obtained in two different ways (1) by re injecting the patient at rest with a second 2 mCi dose of Tl 201 a minimum of 48 hours after the first dose, and (2) by re imaging the heart after a delay of five to 24 hours after the first dose of Tl 201 assuming that the rest redistribution of the initial thallium dose reflected resting myocardial perfusion Reproducibility studies of these two methods were done in six patients, no significant differences were seen in the two images with either normal or diseases coronary arteries Fig 1 shows a postexercise scan and rest redistribution image in a normal patient

Angiography Thirty six of the 38 patients underwent biplane LV cineangiography and selective coronary arteriography using the Judkins technique Patients evaluated to confirm the diagnosis of coronary disease underwent angiography within two days of the treadmill test and scans Of the 17 patients with aortocoronary bypass grafts all of whom had preoperative angiography eight underwent graft visualization and native coronary artery restudy during the same hospitalization as the exercise myocardial scanning LV contraction patterns were characterized in all patients Normal LV contraction was defined by symmetrical contraction in the right and left anterior oblique positions with RAO minor diameter shortening of at least 25 per cent and angiographic ejection fraction of at least 55 per cent [3] The presence of one or more areas of hypokinesia, akinesia or paradoxical wall motion on angiogram and/or enlarged LV size associated with depressed ejection fraction, defined abnormal LV contraction All myocardial scans treadmill tests and angiographic studies were interpreted separately and independently

Results

Group I (Table I) Six of 15 (40 per cent) patients with severe coronary disease had positive treadmill tests seven of 15 (47 per cent) had nondiagnostic treadmill tests and two of 15 (13 per cent) had negative treadmill tests Fourteen of 15 (93 per cent) had positive exercise myocar

Table I Correlative data in 15 patients with severe coronary disease

Patient no	No of vessels and location of CAD	LV function	Treadmill test	Exercise scan	R/E change	Anatomic agreement
1	Single (RCA)	Normal	Negative	Positive	no	yes
2	Single (LAD)	Abnormal	Nondiag	Positive	no	yes
3	Single (LAD)	Abnormal	Negative	Positive	no	yes
4	Single (LCX)	Normal	Nondiag	Positive	yes	yes
5	Single (LAD)	Abnormal	Nondiag	Positive	yes	yes
6	Single (RCA)	Normal	Nondiag	Positive	no	yes
7	Single (LAD)	Normal	Nondiag	Positive	no	yes
8	Single (RCA)	Normal	Positive	Positive	no	yes
9	Single (LAD)	Normal	Positive	Positive	no	yes
10	Double (LAD LCX)	Abnormal	Positive	Negative	no	no
11	Double (LAD RCA)	Abnormal	Nondiag	Positive	no	yes
12	Double (LAD RCA)	Abnormal	Positive	Positive	no	incomplete
13	Triple	Abnormal	Nondiag	Positive	no	incomplete
14	Triple	Abnormal	Positive	Positive	no	yes
15	Triple	Abnormal	Positive	Positive	no	yes

Abbreviations R/E = rest vs exercise RCA = right coronary artery LAD = left anterior descending artery LCX = left circumflex artery CAD = coronary artery disease

Nondiag = nondiagnostic

Right ventricular prominence with exercise only

dial scans and one of 15 (7 per cent) had negative myocardial scans In patients with single vessel coronary disease two of nine (22 per cent) had positive treadmill tests five of nine (56 per cent) had nondiagnostic treadmill tests and two of nine (22 per cent) had negative treadmill tests All nine patients had positive myocardial scans (Fig 2) with excellent correlation between the defect seen on scan in left anterior oblique and lateral views and the affected coronary artery Among patients with severe double and triple vessel coronary disease although there were no false negative stress tests two of six (33 per cent) had nondiagnostic stress tests Five of six (83 per cent) of these patients had positive myocardial scans while one of six had a negative scan (a false negative myocardial scan) Figs 3 and 4 illustrate typical myocardial scans obtained in patients with triple vessel disease The correlation between scan defects and the sites of coronary stenosis was poorer in patients with double and triple vessel disease compared to those with single vessel involvement The scans of such patients were often notable for their diffusely poor uptake of Tl 201 however the uptake and hence the general scan quality obtained after exercise usually exceeded that of the resting scans

Two additional patients with classic effort angina relieved by rest and nitroglycerin were studied with stress tests and myocardial scans only Both patients had positive treadmill tests and myocardial perfusion scans

Group II Four patients had definite coronary disease without any single stenosis exceeding 50 per cent of luminal diameter Three of these patients had mild disease in all three major coronary vessels and one patient had mild two vessel disease' One of the four patients had a positive treadmill test and this patient had a positive myocardial scan Three of these patients had nondiagnostic treadmill tests one had a positive myocardial scan in the presence of normal left ventricular contraction and minimal coronary disease while two of these patients each with more extensive mild coronary disease had negative scans We have considered the positive scan to be a false positive (Fig 5) It is not known whether mild extensive coronary disease always produces abnormal myocardial perfusion and so the negative scans cannot be considered to be definite false negatives

Group III Of three patients with chest pain and normal coronary arteriograms and left ventriculograms treadmill tests were negative in two and nondiagnostic in one All three patients had normal myocardial scans

Group IV (**Table II**) Seventeen patients with aortocoronary bypass grafts were restudied with rest and exercise scans Table II shows that not all significant coronary obstructive lesions were

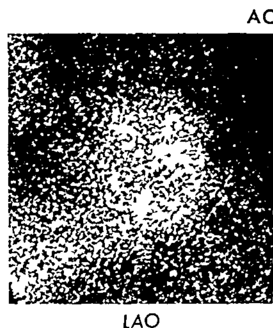


Fig 3 A positive exercise myocardial scan in a patient with triple vessel severe coronary disease Multiple myocardial defects are present

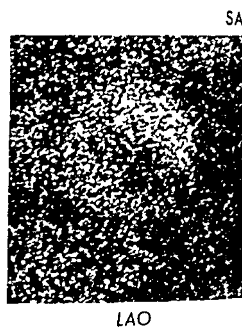


Fig 4 A positive exercise myocardial scan in another patient with triple vessel severe coronary disease Patchy poor myocardial uptake of Tl 201 is noted A discrete defect is also present at the 4 o clock position

Table II Correlative data in 17 patients with aortocoronary bypass grafts

Patient no	*Graft visualized*	*Extent of native CAD*	*No of grafts placed*	*Grafts patent*	*LV function*	*Treadmill*	*Scan*
1	yes	Single	One	One	Abnormal	Nondiag	pos
2	yes	Single	One	None	Normal	Nondiag	pos
3	yes	Double	One	One	Normal	Nondiag	po
4	yes	Double	Two	Two	Abnormal	nondiag	pos
5	yes	Triple	One	One	Abnormal	positive	pos
6	yes	Triple	One	One	Abnormal	positive	ne
7	yes	Triple	Two	One	Normal	nondiag	pos.
8	yes	Triple	Three	Three	Normal	nondiag	neg
9	no	Single	One			nondiag	pos
10	no	Single	One			nondiag	neg
11	no	Single	One			positive	neg
12	no	Single	One			negative	neg
13	no	Double	One			positive	pos
14	no	Double	Two			positive	neg
15	no	Double	Two			nondiag	pos
16	no	Triple	Two			positive	pos
17	no	Triple	Three			positive	pos

Abbreviations CAD = coronary artery disease nondiag = nondiagnostic pos = positive neg = negative

bypassed in this small sample group of patients

Nine of 17 (53 per cent) patients had nondiagnostic treadmill tests, in most cases related to postoperative baseline ST segment changes Eleven of 17 (65 per cent) had positive myocardial scans, but only four of these 11 patients had positive treadmill tests Two of nine patients in whom aortocoronary bypass grafts were not visualized had negative scans and positive treadmill tests both patients had all significant obstructive lesions bypassed and were asymptomatic

All eight patients with graft visualization studies were symptomatic with chest pain Among them six had positive myocardial scans but only one of these six had a positive treadmill

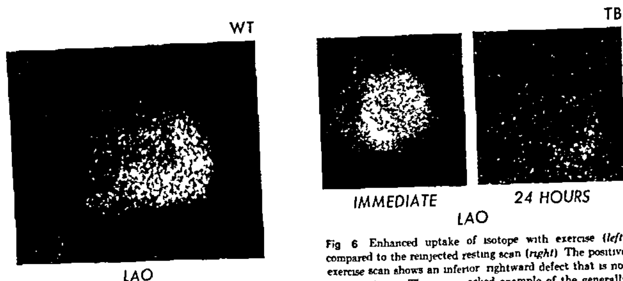


Fig 5 A "false positive" myocardial scan showing a defect located to the left and superiorly in a patient with minimal coronary disease Interpretation of defects in this area may be difficult because of the proximity of the left ventricular outflow tract and great vessels This patient had a non diagnostic treadmill test and anginal chest pain Independent verification of his myocardial perfusion defect is thus unavailable. (*See text*)

Fig 6 Enhanced uptake of isotope with exercise (*left*) compared to the reinjected resting scan (*right*) The positive exercise scan shows an inferior rightward defect that is not present at rest. This is a marked example of the generally poorer uptake of isotope during the resting scan However isotope uptake can be seen at rest in the region of the inferior rightward exercise scan defect. This patient had single vessel coronary disease with a left circumflex artery occlusion

test while five had nondiagnostic stress tests Two of the eight patients had negative myocardial scans One with a positive treadmill test and significant unbypassed native coronary disease probably had a false negative scan The other patient had a nondiagnostic treadmill test three patent grafts and no further unbypassed native coronary disease This is presumably a true negative scan reflecting adequate myocardial perfusion

Patients with positive scans were found to have aortocoronary bypass graft occlusion without significant additional native coronary disease patent grafts with additional unbypassed native coronary lesions or a combination of unbypassed lesions and at least one graft occlusion In two patients one with single and one with double vessel native coronary disease all lesions were bypassed and all grafts were patent yet positive rest and exercise scans were obtained In both patients new abnormal segmental contraction of the left ventricle was found on the postoperative angiogram This represents yet another explanation of a positive scan in post aortocoronary bypass surgery patients

Rest vs exercise scans Only three of the total of 38 patients had resting scans that differed

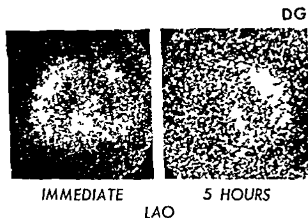


Fig 7 Predominence in right ventricular uptake of isotope after exercise ("omega sign") with a superior septal defect present (*left*) After five hour redistribution of Tl 201 (*right*) the defect is no longer present and the left ventricle is more prominent Reinjection produced similar results This patient has a single patent aortocoronary bypass graft to the left anterior descending artery and a small gradient across the pulmonic valve

distinctly from their exercise scans One patient (Fig 6) with single vessel disease had an inferior defect present with exercise but absent at rest In another patient with a single patent bypass graft to the left anterior descending artery (Fig 7) right ventricular prominence noted with exercise (the "omega sign") was absent at rest This patient had a soft basilar systolic murmur and a

persistent 20 mm Hg gradient from right ventricle to pulmonary artery at catheterization, without electrocardiographic evidence of right ventricular hypertrophy The third patient had single vessel coronary disease and prominent RV uptake of isotope with exercise A scan defect was present both at rest and after exercise

Discussion

Isotopes of potassium (K 43),[4] rubidium (Rb 81)[5] cesium (Cs 129),[6] and thallium (Tl 201)[7] are all concentrated within the cell and allow myocardial images to be made with suitable scanners or gamma cameras The availability of a mobile gamma camera makes it possible to obtain high resolution myocardial images in the tread mill laboratory or at the patient s bedside[1] elimi nating the necessity of transporting the patient to the hospital s Nuclear Medicine Department

All the available isotopes for myocardial scan ning are cyclotron produced Tl 201, because of its low energy emission (69 to 80 kev x rays 95 per cent abundant) and rapid uptake by the myocar dium[7] is the preferred isotope for postexercise imaging with the scintillation camera K 43 and Rb 81 are positron emitters unsuitable for gamma camera imaging without special heavy lead shielding[8] not generally available and making mobility impossible Cs 129 is con centrated too slowly by the myocardium to be useful for exercise imaging[9]

Each of the diagnostic techniques currently used to evaluate coronary artery disease has certain limitations Those of stress electrocar diography have received much attention, and have been recently emphasized[10,11] Both false negative and false positive stress tests may occur frequently for a variety of technical, physiologic, and demographic reasons Among our Group I patients two of 15 had false negative treadmill tests It has been suggested that false negative treadmill tests are more likely in single vessel as opposed to multiple vessel coronary disease[12], both patients had single vessel disease While it is impossible to accurately define the sensitivity and specificity of either treadmill tests or the myocar dial scans from our limited data the fact that seven of 15 patients with severe coronary disease three of four patients with mild coronary disease nine of 17 postaortocoronary bypass patients and one of three normal patients had *nondiagnostic* treadmill tests suggests the potential utility of an additional noninvasive test

Coronary arteriography has been employed as the standard diagnostic procedure against which other tests for the detection of coronary disease are measured While technically good coronary arteriography (an 'anatomic test) may accu rately define the presence or absence of coronary lesions, it is not always clear that normal coro nary arteries exclude the presence of ischemic heart disease[14] or invalidate a ' positive myocar dial perfusion scan (a ' functional test) Indepen dent verification of the status of myocardial perfusion is not readily available in the clinical setting Moreover, the hemodynamic significance and perfusion deficit due to a given coronary lesion may not be accurately predicted Experi mental evidence correlating coronary blood flow and regional myocardial perfusion using isotope techniques suggests that obstructive lesions up to 85 per cent luminal diameter may not alter resting flow and perfusion[15] Incremental but subtotal stenosis of coronary arteries in dogs results in non linear reductions of myocardial perfusion proportional to but less than the per cent decrease in coronary blood flow[16] In two of our patients definite but mild coronary disease was present left ventricular contraction was normal, and myocardial perfusion scans were normal Two other patients had positive scans one with mild coronary disease in two vessels normal ventricular contraction and a positive treadmill test and the other with minimal coro nary disease normal ventricular contraction and a nondiagnostic treadmill test We have chosen to call the latter a false positive scan but it should be emphasized that using a measure of myocar dial perfusion such as scanning to extrapolate back to the location and extent of coronary lesions can be fraught with error This problem is underscored by our findings in aortocoronary bypass patients (*vide infra*) in whom various combinations of graft patency and occlusion native coronary disease and left ventricular contraction patterns may be responsible for posi tive scans

Previously reported results of post exercise myocardial perfusion scanning suggest a high sensitivity of this technique in detecting coronary disease[2,8,17,18] and are similar to our findings in Group I patients 100 per cent of our Group I

patients with single vessel disease had discretely positive myocardial scans with good anatomic localization of coronary disease Eighty three per cent of patients with double and triple vessel coronary disease had positive scans with poorer anatomic correlation Only one of 15 Group I patients had a false negative scan Attention to Tl 201 injection technique correct timing of the injection at peak exercise and flushing of the isotope bolus with saline are important in eliminating technical inadequacy as a source of false negative myocardial scans

It must be emphasized that Tl 201 is not the ideal myocardial scanning agent Its low energy can impair the resolution of images significantly in the resting patient Since myocardial blood flow is relatively increased and hepatic blood flow relatively decreased during exercise isotope uptake by the myocardium is often greater during exercise than at rest Consequently exercise which can bring out scan defects by inducing myocardial ischemia can also enhance the clarity and definition of scan images Resting vs exercise comparisons therefore may not only be difficult to make but also yield less meaningful information In contrast to other reports[2, 4] we have not found resting vs exercise scan changes to be helpful in detecting coronary disease or in distinguishing prior myocardial infarction from coronary stenosis We found this to be the case whether re injection or reimaging methods were used for obtaining resting myocardial scans It is also important to note that not only discrete scan defects but generalized low isotope uptake low count rates and patchy images may represent positive scans rather than artifact or deficient injection of isotope This is especially true in the presence of triple vessel coronary disease

The evaluation of aortocoronary bypass graft status and postoperative myocardial perfusion constitute obvious applications of myocardial scanning Several studies using various isotopes and methods have addressed this problem[9, 4] In our patients positive myocardial scans could be attributed to graft occlusion significant unbypassed native coronary lesions combinations of these situations or regional abnormalities of left ventricular contraction The last might indicate prior myocardial infarction a situation in which Tl 201 has proven diagnostically useful[1, 25, 2] We were unable to further discriminate the status of bypass grafts by the localization of scan defects or by rest vs exercise changes in myocardial isotope uptake

Summary

Post exercise myocardial scanning with thallium 201 provides an additional noninvasive technique for the detection of coronary artery disease which may be especially useful in situations where treadmill testing is likely to be nondiagnostic Tl 201 scans are sensitive in the presence of severe discrete single vessel coronary disease or extensive diffuse triple vessel disease In addition perfusion scanning provides an estimate of regional flow deficits in the myocardium complementary to the anatomic information derived from arteriography and supplementary to the functional information obtained from stress testing However our present inability to independently corroborate the status of myocardial perfusion in the clinical setting somewhat limits the value of this information

In this series 20 of 42 treadmill tests were nondiagnostic while 2 of 15 patients with severe coronary disease had false negative treadmill tests Nine of nine patients with single vessel coronary disease had positive myocardial scans with good anatomic correlation between the location of the scan defect and the site of anatomic disease on angiogram Eighty three per cent of patients with double and triple vessel disease had positive scans although anatomic correlation was poorer in these cases Despite the theoretical advantages of performing both rest and exercise scans such comparisons were found to be of limited value using this isotope in the clinical setting The very differences in blood flow and hence isotope uptake which should account for rest vs exercise changes in the presence of ischemic disease and the low energy of emission of Tl 201 led to poor image clarity and resolution at rest Underlying segmental wall motion abnormalities at rest could not always be excluded as the cause of a scan defect exercise rarely altered such a defect recognizably No false positive but one false negative scan was obtained among patients with severe coronary disease

The role of Tl 201 myocardial perfusion scanning in detecting mild coronary disease and in evaluating postoperative graft status remains uncertain The effect on perfusion of mild coro

nary obstructive lesions cannot be accurately predicted One patient, with minimal coronary disease and normal ventricular contraction had a positive myocardial scan, this was considered to be a false positive Among post aortocoronary bypass patients, positive scans related to graft occlusion, significant unbypassed native coronary disease, segmental ventricular wall motion abnormalities or a combination of these factors

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The small coronary arteries in alcoholic cardiomyopathy

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The myocardium is nourished by the smallest blood vessels—capillaries. Blood reaches the capillaries through small arteries. The fact that the interest of cardiologists is presently directed at the large coronary arteries instead of the small ones is understandable since these large arteries which course along the surface of the heart are the main channels of the coronary system. They deliver blood to the more peripherally oriented smaller vessels. But these small vessels are directly involved with supplying the myocardium with blood and therefore should not be ignored. Full patency of the large coronary arteries does not necessarily indicate full patency of the small peripheral vessels nor does a normal coronary angiogram exclude disease of the smaller arteries. This fact is too often ignored in clinical practice.

This report is concerned with an *in vitro* study by x ray angiographic technic of the coronary arterial system of two patients with alcoholic cardiomyopathy with special emphasis on the small peripheral coronary arterial system of the myocardium of both ventricles.

Materials and methods

One hundred and fifty eight hearts were collected at autopsy from the New Orleans Veterans Administration Hospital, the Charity Hospital of Louisiana in New Orleans and from the New Orleans Coroner's Office for the study of the coronary arterial blood vessels. The hearts were collected at random and were all prepared and studied in the same manner. The patients had miscellaneous diseases not necessarily cardiac disease. Two of the patients had alcoholic cardiomyopathy and their hearts were studied closely for coronary vasculature and are described in this report.

The hearts were fresh and whole and were studied within a few hours of death never beyond 24 hours after death. The hearts were collected as soon as possible after removal from the body and were immediately washed and x ray views of the intact unopened heart were obtained. The two coronary arterial vessels were rinsed with warm normal saline (0 85 per cent NaCl in H_2O) at 120 to 150 mm Hg pressure until the vessels were cleared of all gross evidence of blood as described previously from this laboratory[1] and by Fulton[3] The arterial system was then filled with a suspension of 20 per cent Micropaque in 10 per cent formalin at 100 mm Hg pressure using an injection apparatus as described by Fulton[2,3] The hearts were then cooled rapidly in ice and fixed in formalin for 30 to 60 days to allow the formalin to penetrate and fix the entire myocardium with the barium in the coronary arterial system.

After fixation in formalin the hearts were thoroughly washed with tap water cut and unrolled as described by Fulton[2,3] The open ventricles were then exposed to soft x ray using a Model 6191 Picker industrial machine. Exposure times of 40 to 45 minutes per side with settings of 7 ma and 28 Kv were required. Kodak fine grain positive film 5 by 7 inches without cassettes was used. X ray stereograms were prepared by x

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raying each heart two times, once with the film angled 3 degrees to the right from the axial ray on an inclined board and once with the film angled 3 degrees to the left[1] The ventricles were then sliced (approximately 5 mm thick) from apex to base with the knife parallel to the atrioventricular zone These slices were also x rayed for stereograms as described above

Patient No 1 H H, a 60 year old alcoholic man, was admitted to the V A Hospital in New Orleans because of increasing mental confusion and lethargy The patient had a history of excessive alcohol consumption for more than 30 years

Physical examination on admission to hospital revealed a blood pressure of 150/100 mm Hg a pulse rate of 90 beats per minute a respiratory rate of 20 per minute, and a temperature of 98 6° F The patient was mentally confused and had a flapping tremor The sclerae were mildly icteric The remainder of the physical examination was reported as being within normal limits

The electrocardiogram showed sinus tachycardia left axis deviation, and poor R wave progression from V_1 to V_3 The T wave was slightly low in Lead I and isoelectric in Lead III

The patient was treated for hepatic coma during the period of hospitalization However, he failed to respond to treatment and died 21 days after admission

At necropsy, the heart weighed 490 Gm Cardiac measurements were left ventricular wall thickness, 14 mm, right ventricular wall thickness 7 mm, mitral valve circumference 85 mm tricuspid valve circumference, 87 mm aortic valve circumference 64 mm, and pulmonic valve circumference 65 mm No gross scarring or other lesions were present Examination of myocardial sections by light microscopy revealed fatty infiltration of the right atrial myocardium and mild focal interstitial fibrosis with atrophy of muscle fibers in the left ventricular myocardium

Patient No 2 E K a 42 year old man was admitted to the V A Hospital in New Orleans with a long history of alcoholic cirrhosis and most recently, increasing ascites requiring treatment with diuretics He was admitted to the hospital because of increasing abdominal swelling, nausea and vomiting

Physical examination on admission revealed a blood pressure of 100/70 mm Hg a pulse rate of 84 beats per minute and a temperature of 97° F The sclerae were icteric and multiple spider angiomata were present on examination of the skin A Grade II systolic murmur was present at the cardiac apex The remainder of the physical examination was reported as being within normal limits

Laboratory work on admission revealed a hemoglobin of 11 2 Gm per cent and a hematocrit of 33 per cent The serum bilirubin was 3 8mg per cent and the albumin 3 0 Gm per cent The sodium was 118 mEq /L The remainder of the blood chemistries were within normal limits

Chest x rays were obtained with the patient in the recumbent position rendering accurate cardiac evaluation impossible Electrocardiograms revealed diffuse abnormalities of the ST segments and T waves, with some notching and slurring of the QRS complexes, compatible with diffuse myocardial disease

Following admission to the hospital the patient was treated for possible intestinal obstruction However he soon began to develop hepatic encephalopathy which was unresponsive to therapy The patient died 37 days after admission to the hospital

At necropsy the heart weighed 470 Gm Cardiac measurements were left ventricular wall thickness 19 mm, right ventricular wall thickness 8 mm mitral valve circumference 100 mm tricuspid valve circumference 110 mm aortic valve circumference 50 mm, pulmonic valve circumference, 55 mm Grossly the heart was enlarged but no other abnormalities were noted Examination of myocardial sections by light microscopy revealed no specific pathologic findings

Results

Figs 1 to 7 best illustrate the organization and three dimensional spatial orientation of the peripheral or small arterial vessels of the myocardium of the ventricles of the two hearts of the patients with alcoholic cardiomyopathy The small arteries which branch off from the main coronary arterial vessels located on the surface of the heart are spatially oriented in different manners for the free wall of the left ventricle the free wall of the right ventricle and the interventricular septum at the apical region of the heart and at the basal regions near the atrioventricular groove These arterial systems are briefly discussed below



Fig 1 Radiographic view of the coronary artery system of the whole heart which is laid open as described by Fulton to display the vessels

Free wall of the left ventricle The small arteries which penetrate into the left ventricular myocardium branch from the large surface coronary arteries like trunks of trees (Figs 2 3 and 4) This tree like arrangement has been previously described The branches of these "trees branch dichotomously and connect (anastomose) with the branches of the adjacent arterial trees located all around them The trunks (main arteries) of the surrounding trees are spatially oriented as shown in Figs 2 and 3 The arterial trees resemble trees in winter without their leaves (Fig 5)

The arterial supply to the papillary muscle system which is attached to the internal surface of the left ventricle has been described in detail previously[7] The observations in these investigations merely confirm the previous findings Briefly the finger type of papillary muscle is supplied with a single central artery[7] or one tree from which small arterial branches are three dimensionally oriented throughout the papillary muscle (Fig 4) This central artery originates from the main coronary arterial vessels on the surface of the heart The papillary muscle which is tethered has a different type of small arterial system[7] The arterial system for tethered papillary muscles comprises parts of arterial trees which stem from the large arteries on the epicardial surface The arrangement provides for a rich blood supply with an abundance of anastomoses within the entire myocardium of the left ventricle and the papillary muscle system Each muscle fiber is supplied with a small twig of the trees terminal vessels in a sense The subendocardial myocardium and especially the papillary muscles receive their blood supply from the greatest distance—from the aortic origin of the coronary arteries

The trabeculae carneae receive their arterial system as branches of the coronary arterial trees which originate from the large epicardial coronary arteries There is an abundance of anastomoses within the trabeculae carneae A fairly large coronary artery courses longitudinally along the crest of the trabeculae carneae This vessel anastomoses with other smaller arteries which originate from the penetrating more vertically oriented trees

The coronary arterial system at the apical region of the heart is arranged differently from that at the base in the region of the atrioventricular groove (Figs 1 and 2) At the apical region of the heart there is a tendency for the arteries to form fewer tree units" and more of a network or mesh of arteries which anastomose with the branches of the anterior and posterior descending coronary arteries thereby connecting these two descending arteries This network of arteries located near the epicardial region of the apex

RADIOGRAPHIC VIEW OF SMALL MYOCARDIAL ARTERIES
(ALCOHOLIC CARDIOMYOPATHY)

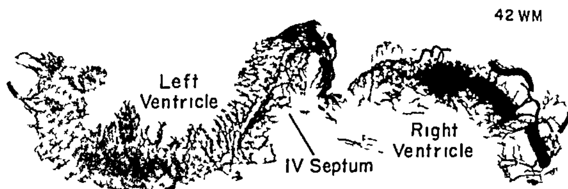


Fig 2 Radiographic view of the small myocardial arteries in a 5 mm thick slice of the heart shown in *Fig 1* This slice was cut about midway between the apex and the A V groove

STEREOSCOPIC VIEWS OF SMALL MYOCARDIAL ARTERIES
(Free Wall of Left Ventricle)

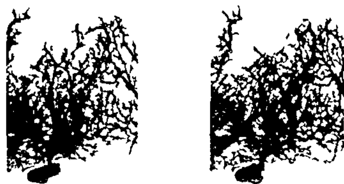


Fig 3 Stereoscopic views of a segment of the myocardium of the free wall of the left ventricle of the same heart as in *Figs 1* and *2* showing the spatial relationships of the numerous small arteries which supply that segment of the left ventricle

STEREOSCOPIC VIEWS OF SMALL MYOCARDIAL ARTERIES
(Papillary Muscle)



Fig 4 Stereoscopic views of a segment of the myocardium of the anterolateral papillary muscle of the left ventricle showing the spatial relationships of the numerous small arteries which supply the papillary muscle

sends penetrating branches to the endocardial surface (Figs 1 and 2) The larger vessels tend to course parallel with the epicardial and endocardial surfaces of the heart (Figs 1 and 2)

Arteries in the region of the atrioventricular groove also tend to lose the tree unit formation These arteries course parallel with the A V groove sending penetrating branches into the myocardium in a less uniform manner (Figs 1 and 2) Anastomoses are well developed in the region of the A V groove

In general the distribution and spatial orientation of the smaller arterial system and the large epicardial coronary arterial channels in the patients with alcoholic cardiomyopathy were normal Their luminal surfaces were smooth In general all the arteries tended to be slightly dilated in comparison to the normal arteries[4]

The arterial supply to the left ventricle was much richer than that to the right ventricle as previously reported decades ago by Fulton and others [3,5,9] In spite of dilatation and hyper

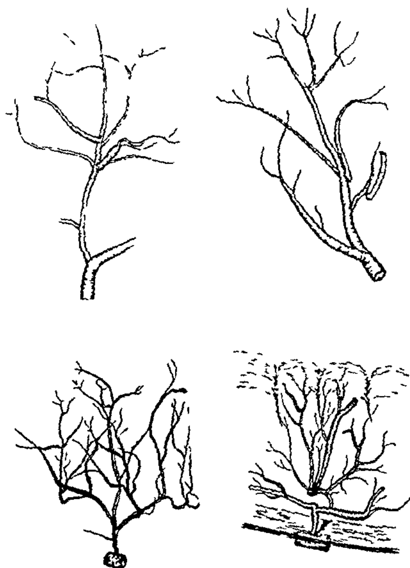


Fig 5 Diagrammatic reproductions of four representative winter tree configurations selected from the free wall of the left ventricle of injected hearts The configurations vary considerably

trophy of the entire heart in alcoholic cardiomyopathy the arterial system was well distributed throughout the musculature There were no areas in which the myocardium did not have an abundance of arteries

Right ventricle The supply of small coronary arteries to the right ventricle is quite different from that to the left ventricle The small arteries branch off the larger trunks coursing along the surface of the heart The tree units are less numerous and less well developed The vessels tend to course more parallel to the epicardial and endocardial surfaces of the right ventricular wall The supply of small arteries is less rich in comparison to that for the left ventricle However the longitudinally coursing small arteries are more tortuous and spiral apparently to accommodate the changes in size of the right ventricle during the cardiac cycle and to compensate for the absence of well developed tree units (Fig 6) The small arteries connect with those of the left ventricle at the apex within the septum and at the interventricular groove or any point where the two ventricles are in direct contact (Figs 1 and 2)

From the small arteries extremely numerous fine hair like arteries branch off parallel to each other and course perpendicular to the epicardial

STEREOSCOPIC VIEWS OF
SMALL MYOCARDIAL ARTERIES
(Free Wall of Right Ventricle)



Fig 6 Stereoscopic views of a segment of the free wall of the right ventricle of the same heart as in *Figs 1* and *2* showing the spatial orientation of the small arteries supplying the right ventricular myocardium

STEREOSCOPIC VIEWS OF
SMALL MYOCARDIAL ARTERIES
(Interventricular Septum)



Fig 7 Stereoscopic views of the septum of the slice of myocardium shown in *Fig 2* The main arterial trunks course parallel to the endocardial surfaces through the septum Consult text for details

surface of the right ventricle These many fine arteries produce a brush like appearance (Fig 2) not observed in the left ventricle

The numerous well developed trabeculae carneae of the right ventricle have a supply of small arteries comparable to that in the left ventricle But here as well as in the papillary muscle of the right ventricle the small arteries are not as numerous The small arteries anastomose freely to ensure a good collateral circulation

General remarks

The arterial supply to the myocardium of the two patients with alcoholic cardiomyopathy was extremely good No arteriosclerotic plaques were present a situation quite different from the hearts of patients with ischemic cardiomyopathy In fact the normal arterial distribution to the heart is readily studied in the hearts of patients with alcoholic cardiomyopathy Previous investigators have commented on the remarkable absence of atherosclerotic changes in the large coronary arteries of patients with alcoholism in general[11] and with alcoholic cardiomyopathy in particular[1, 13] For example a postmortem study of the hearts of 97 alcoholic patients revealed no coronary atherosclerosis in 36 (37 per cent) a slight atherosclerosis in 49 (51 per cent), moderate changes in 6 (6 per cent) and marked changes in 6 (6 per cent)[11] Necropsy findings in 10 patients with primary myocardial disease most of whom were alcoholics revealed absence of arteriosclerosis in five hearts negligible or mild arteriosclerosis in two and moderate arteriosclerosis in three patients[12] Some reports have described changes in small branches of the coronary arteries composed of subintimal plaques of homogeneous reddish smudgy material[13] However these changes were observed in patients with far advanced cardiomyopathy whereas the patients in our study had relatively early disease Thus it would seem that pathology of the small coronary arteries is not necessary for the development of alcoholic cardiomyopathy

This study revealed the coronary circulatory tree unit which was described over 30 years ago by Gross and Kugel[5] and more recently by Fulton[7] Careful consideration of these three

dimensional units clearly reveals how ideal they are for a structure such as the heart which contracts and dilates about 75 times or more per minute continuously for many years This spatial organization was well developed with fully patent vessels in our two patients with alcoholic cardio myopathy There was no evidence of destruction or interruption of the small coronary arteries in these patients In spite of the dilated and hyper trophied state of the two ventricles the small coronary arteries reached the subendocardial myocardium and the myocardium of the papil lary muscles and the trabeculae carneae Thus the abnormal T waves recorded from these patients could not have been produced by disease of the small coronary arteries as far as this study is concerned As the ventricles dilated and extended the small coronary arteries reached out further This growth of the arterial system is not only interesting but challenges one s imagination as to the mechanism and stimuli responsible for the growth and extension of the coronary arterial system into the greater mass of myocardium which was also centrifugally displaced with dila tation

The tree like circulatory units are interesting and intriguing For convenience they will be called tree units Their architectural and func tional beauty can only be appreciated from a careful study of the stereoscopic photographs of the injected vessels (Figs 3 4 and 6) This is simple if one imagines the free wall of the left ventricle to be lying flat with the epicardial surface on a table and the endocardial surface directed upward The vessels would then resemble an orchard of evenly planted or spatially oriented trees with the tips of their branches touching each other With little imagination and with a knowl edge of the microcirculation of the myocardium it is easy to visualize the manner in which the tips of the branches of the trees supply blood to the arterioles capillaries and vessels and small micro circulatory anastomoses The branches there fore interconnect to provide an effective collat eral circulation should the trunk to any tree become obstructed This *tree orchard* orienta tion makes it possible for the myocardium to contract and dilate without necessarily kinking or obstructing the lumen of the small coronary arteries or traumatizing their walls excessively This spatial morphologic arrangement and orien tation is not only extremely interesting and unique but necessary to assure least trauma to the vessels

The interconnecting and anastomotic relation ships were so extensive that arrest of flow in one circulatory tree unit could occur and blood would still be supplied to the ischemic unit by means of anastomoses with several immediately adjacent units This tree pattern is highly devel oped in the left ventricle (Figs 2 and 3) It is less well developed near the A V groove in the area of the apex and in the right ventricle (Figs 2 and 6) Figs 1 2 3 4 and 6 readily reveal how these trees with their branches and the arteries in the trabeculae carneae make it possible for the arteries to fold i.e for the branches of the trees to move centripetally toward the main trunk of the trees during cardiac systole and to unfold or spread out centrifugally during diastole of the ventricles This spatial orientation and architec ture of the coronary arterial *system is quite* unique and serves the purpose of maintaining adequate arterial supply to the myocardium without being injured or traumatized in spite of trillions of cardiac contractions and dilatations

The supply of small arteries to the right ventricle is not nearly as luxurious as that for the *left side of the* septum and free wall of the left ventricle nor are the tree formations and spatial orientations nearly as well developed (Figs 2 and 6) The arteries in the right ventricular myocar dium are tortuous and coil as they do in the left *ventricle* and possibly even more so since changes in the wall size during the cardiac cycle have to depend mainly on such non linear courses of the arteries and less upon the morphology of tree configurations

The circulation of the septum is also rather *interesting* Large arteries penetrate the septum at about one third of its thickness from the right ventricle or two thirds from the endocardial surface of the left ventricle The arterial supply to the left side (two thirds) of the septum is richer than that to the right side (one third) The tree type of arterial distribution is predominantly to the left side of the septum On the right side of the septum the branching distribution and spatial orientation of the arteries are more like that of the free wall of the right ventricle (Fig 7) Thus these anatomic arterial patterns indicate that a large part (two thirds) of the septal myocardium does belong *to the left* ventricle and a smaller part (one third) belongs to the right ventricle

The septum, therefore, is not entirely left ventricular myocardium

The arterial supply to the fat of the surface of the heart is achieved by means of many very small hair like arteries which extend vertically from the large vessels to the epicardial epithelium (Fig 2)

Summary

The small coronary arteries of two patients with alcoholic cardiomyopathy were studied by means of fine particle barium injection and soft x ray technic The spatial architecture of these small arteries which penetrated into the depth of the right and left ventricular myocardium were normal Their lumina were somewhat dilated and their luminal surfaces were smooth The tree circulatory units' were described from this study and were found to be normal The left ventricular myocardium was richly supplied with small arteries whereas the myocardium of the right ventricle was not so richly supplied The myocardium of the papillary muscles and the trabeculae carneae of the left ventricle also had a good supply of small arteries as did the remote endocardial myocardial appendages Numerous fine hair like arteries extended to the epicardial myocardium of the right ventricle to form a brush like appearance

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Lenegre's disease in youth

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Primary A V block that is block without other evidence of organic heart disease[1,2] is a well known entity It was first put on a sound pathologic basis by Lenegre and by Lev[3] who reported sclerodegenerative changes in the bundle branch system in hearts from affected patients Rosenbaum and associates defined two subgroups designated Lenergre s Disease and Lev s Disease respectively In the former the sclerodegenerative changes are of unknown etiology and occur principally in young and middle aged adults In the latter the observed changes are thought to be secondary to fibrosis and calcification of the cardiac skeleton related to the aging process and are largely confined to older age groups Lenegre s disease is generally the more progressive and frequently results in advanced or complete A V block Lev s disease also may progress to complete block but the course is more protracted Dhingra and colleagues have recently suggested the following criteria for antemortem diagnosis of Lenegre s and Lev s diseases (1) development of progressive intraventricular conduction delays eventuating in complete heart block (2) a site of block distal to His bundle and (3) absence of demonstrable organic heart disease Young and middle aged adults fulfilling these criteria would fall into the category of Lenegre s disease older age groups into the category of Lev s disease

Lenegre s disease is of particular import because of its potential for causing symptomatic A V block in the prime of life The age of earliest onset is unknown There are no reported instances in childhood and very few cases have been described in young adulthood The paucity of cases may stem in part from a lack of clearly defined antemortem diagnostic criteria and in part from the lack of routine electrocardiographic studies in the younger age groups The youngest patient described to date was 21 years of age at the time when conduction system abnormalities were first noted and was 31 before the appearance of trifascicular block An increase in the number of well documented cases in younger age groups would improve our understanding of the natural history of the disorder

This report describes the case of a young athletically inclined male without known heart disease who presented with activity related lightheadedness at age 19 and dizziness and fatigue at age 21 Standard electrocardiograms revealed left anterior divisional block and right bundle branch block with intermittent P R prolongation Re evaluation eight months later revealed fixed incomplete trifascicular block with intermittent advanced A V block The clinical and electrocardiographic characteristics together with alterations in the His bundle electrograms appear typical of Lenegre s disease[1,3,4] To our knowledge this is the youngest reported patient with advanced A V block due to this cause Possible electrophysiologic bases of block and exercise induced improvement in A V conduction also are considered

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The septum, therefore is not entirely left ventricular myocardium

The arterial supply to the fat of the surface of the heart is achieved by means of many very small hair like arteries which extend vertically from the large vessels to the epicardial epithelium (Fig 2)

Summary

The small coronary arteries of two patients with alcoholic cardiomyopathy were studied by means of fine particle barium injection and soft x ray technic The spatial architecture of these small arteries which penetrated into the depth of the right and left ventricular myocardium were normal Their lumina were somewhat dilated and their luminal surfaces were smooth The tree circulatory units were described from this study and were found to be normal The left ventricular myocardium was richly supplied with small arteries, whereas the myocardium of the right ventricle was not so richly supplied The myocardium of the papillary muscles and the trabeculae carneae of the left ventricle also had a good supply of small arteries, as did the remote endo cardial myocardial appendages Numerous fine hair like arteries extended to the epicardial myocardium of the right ventricle to form a brush like appearance

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13 Pintar K Wolanskyj B M and Gubbay E R Alcoholic cardiomyopathy Can Med Assoc J 93 103 1965

Case reports

Lenegre's disease in youth

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Primary A V block, that is, block without other evidence of organic heart disease, is a well known entity. It was first put on a sound pathologic basis by Lenegre and by Lev,[2] who reported sclerodegenerative changes in the bundle branch system in hearts from affected patients. Rosenbaum and associates defined two subgroups designated Lenegre's Disease and Lev's Disease, respectively. In the former, the sclerodegenerative changes are of unknown etiology and occur principally in young and middle aged adults. In the latter, the observed changes are thought to be secondary to fibrosis and calcification of the cardiac skeleton related to the aging process and are largely confined to older age groups. Lenegre's disease is generally the more progressive and frequently results in advanced or complete A V block. Lev's disease also may progress to complete block but the course is more protracted. Dhingra and colleagues have recently suggested the following criteria for antemortem diagnosis of Lenegre's and Lev's diseases: (1) development of progressive intraventricular conduction delays eventuating in complete heart block, (2) a site of block distal to His bundle, and (3) absence of demonstrable organic heart disease. Young and middle aged adults fulfilling these criteria would fall into the category of Lenegre's disease, older age groups into the category of Lev's disease.

Lenegre's disease is of particular import because of its potential for causing symptomatic A V block in the prime of life. The age of earliest onset is *unknown*. There are no reported instances in childhood and very few cases have been described in young adulthood. The paucity of cases may stem in part from a lack of clearly defined antemortem diagnostic criteria and in part from the lack of routine electrocardiographic studies in the younger age groups. The youngest patient described to date was 21 years of age at the time when conduction system abnormalities were first noted and was 31 before the appearance of trifascicular block. An increase in the number of well-documented cases in younger age groups would improve our understanding of the natural history of the disorder.

This report describes the case of a young athletically inclined male without known heart disease who presented with activity related lightheadedness at age 19 and dizziness and fatigue at age 21. Standard electrocardiograms revealed left anterior divisional block and right bundle branch block with intermittent P R prolongation. Re-evaluation eight months later revealed fixed incomplete trifascicular block with intermittent advanced A V block. The clinical and electrocardiographic characteristics together with alterations in the His bundle electrograms appear typical of Lenegre's disease. To our knowledge this is the youngest reported patient with advanced A V block due to this cause. Possible electrophysiologic bases of block and exercise induced improvement in A V conduction also are considered.

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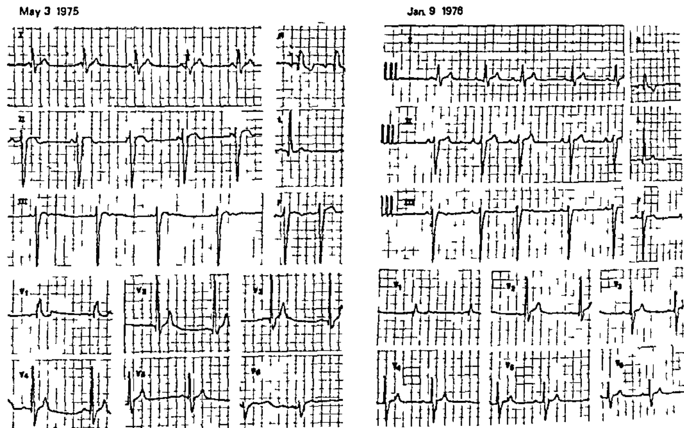


Fig 1 *Panels A and B* show two standard 12 lead electrocardiograms obtained on May 3 19/5 and January 9 1976 respectively Records in *A* were taken on a conventional single channel direct writer machine which records leads sequentially those in *B* were made on a machine which records three leads simultaneously Note the sinus arrhythmia and bradycardia with intermittent A V dissociation due to escape of a junctional pacemaker firing at a normal rate Both records demonstrate left anterior divisional block and right bundle branch block *In Panel A* P R interval duration is 0 20 to 0 22 sec *In Panel B* P R has become more prolonged (0 21 to 0 24 sec) See text for discussion

Case report

The patient is a 22 year old athletically inclined white male who was referred to Northwestern Memorial Hospital for evaluation because of a progressive increase in exercise related dizziness and fatigue over an eight month period commencing in May 1975 Careful questioning revealed that he had probably begun to experience occasional mild dizziness in conjunction with strenuous exercise some two years earlier at age 19 Increases in symptoms compelled him to seek medical attention which he did for the first time in May 1975 (age 21) Routine ECG s at a local community hospital demonstrated sinus arrhythmia and bradycardia with intermittent A V dissociation due to escape of an A V junctional pacemaker and intermittent incomplete trifascicular block (Fig 1*A*) Evidence of more advanced degrees of A V block was not elicited despite suggestive symptoms The patient was discharged with instructions to discontinue his longstanding participation in active sports and to limit other activities insofar as possible Exercise related dizziness and fatigue progressed rapidly over the succeeding months with resultant referral for evaluation of the status of the A V conduction system By the time of his admission to Northwestern Memorial Hospital (January 1976) progression of symptoms had forced him to give up sports and to drastically curtail job related exertion

Physical examination on admission revealed an alert healthy appearing white male looking his stated age Blood pressure was 140/70 The peripheral pulse rate was irregular and averaged 35/minute A fourth heart sound was heard at the apex and a Grade II/IV nonradiating systolic ejection murmur was noted along the left sternal edge The examina tion was otherwise unremarkable Chest x ray and cardiac fluoroscopy revealed only a borderline increase in cardiac silhouette There was no evidence of calcification Echocar diographic studies were normal

Physical examination and electrocardiographic screening of the patient s immediate family (father mother and two brothers) did not reveal evidence of intrinsic heart disease or A V conduction disturbances

Standard electrocardiograms Twelve lead electrocardio grams in Figs 1*A* and *B* were taken on May 3 19/5 and on January 9 1976 respectively The former shows marked sinus arrhythmia and bradycardia with intermittent A V dissocia tion due to escape of an A V junctional pacemaker firing at a normal rate of 50/minute with evidence of intermittent borderline trifascicular block (right bundle branch block and left anterior divisional block with P R intervals of 0 20 to 0.22 sec in duration) The record in Fig 1*B* which was obtained at the time of his admission to Northwestern Memorial Hospital shows interim progression of the A V conduction disturbance as evidenced by further increase in P R (0 21 to 0 24 sec)

Holter monitoring Since standard electrocardiograms failed to demonstrate specific mechanisms underlying stress and activity related dizziness and fatigue the patient was Holter monitored for twelve hours Monitoring records in Figs 2 and 3 were obtained on the same day (1/9/76) as was the

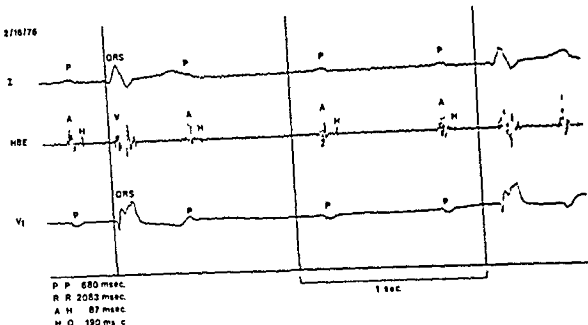


Fig. 4. Simultaneously recorded standard ECG Leads I and V1 and His bundle electrogram (HBE) during period of 3:1 A-V block. P and QRS are labelled on surface leads. Atrial, His and ventricular complexes of intracardiac electrograms are designated "A," "H" and "V" respectively. Each atrial complex of the electrogram is followed by an H potential at a normal A-H interval. The H-Q interval of conducted beats is greatly prolonged. Average values (10 beats) for atrial and ventricular rates and A-H and H-Q intervals are as indicated. Electrogram retouched for clarity. Vertical time lines are 1000 msec apart. See text for discussion.

site of block with prolonged H-Q intervals provide additional evidence in this regard.[1] The age at the time of the initial presentation makes him the youngest reported patient with this condition.[3] The reported occurrence of dizziness two years earlier indicates that advanced conduction system disease may already have been present at age 19. The age of onset of the disease process is unknown but presumably dates to a still younger age.

Although the extent of the conduction system involvement cannot be defined antemortem, the bundle branches appear not to be the only affected structures. It may be inferred from the failure of ventricular escapes to appear during periods of sustained reduction in rate to as low as 29/minute that the peripheral Purkinje system also was involved by the disease process. The implications of the failure of A-V junctional escapes to appear during block induced bradyarrhythmia are less clear. Since development of advanced A-V block generally occurred in conjunction with sinus rates greater than the normal junctional escape rate, absence of escapes under such circumstances can be explained in terms of the depressive effects of concealed conduction of sinus impulses on A-V junctional pacemaker activity[11] rather than intrinsic disease. Occurrence of junctional escapes at normal firing rates (45 to 60/minute) during periods of sinus bradycardia (Figs. 1A to 2B) and the absence of split His potentials in the intracardiac electrograms (Fig. 4) also militate against significant His disease. Irrespective of cause, however, failure of A-V junctional escapes to appear during periods of block greatly accentuated risks attendant upon distal conduction system disease necessitating pacemaker implantation. The His-Purkinje system aside, findings of sinus bradycardia suggest the possibility of concomitant S-A nodal disease. However, the patient's athletic conditioning and regular participation in active sports provide an alternate explanation. The normal sinus rate response to exertion (Fig. 3) also detracts from this possibility.

The development of ventricular ectopy and unexpected transient increase in ventricular rate observed in conjunction with vigorous exertion (Figs. 3A and B) presumably was due to the actions of cathecholamines and is of interest in light of the known effects of these agents on automaticity and conduction in cardiac fibers.[2, 3] Ectopy comes as no great surprise since enhancement of automaticity of latent pacemaker cells

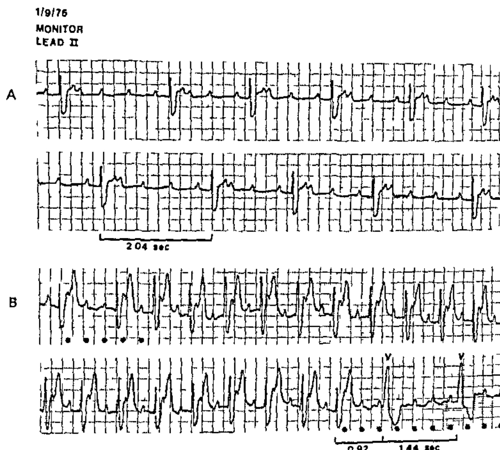


Fig 3 *Panels A and B* show additional monitoring records obtained on the same date as those shown in Fig 2 Strips in each panel are continuous In *Panel A* increases in atrial rate to 130/minute resulted in development of advanced A V block Note failure of ectopic escape beats to occur despite decrease in ventricular rate to 29/minute (cycle length = 2 04 seconds) *Panel B* shows improvement in A V conduction during period of exercise induced sinus tachycardia (sinus rate = 180/minute) Note decrease in degree of block to 2 1 with corresponding increase in ventricular rate (to 90/minute) Dots at beginning and end of record identify atrial activity In contrast to previous records also note appearance of accelerated ventricular escapes (V) (cycle lengths = 0 92 + 1 44 seconds) Defaced portions of grid retouched See text for discussion

of Scherlag and colleagues The patient exhibited predominantly advanced degrees of A V block during catheterization Fig 4 shows records obtained during a period of 3 1 A V block (atrial and ventricular cycles averaged over 10 beats equaled 680 and 2083 msec respectively) It will be seen that each atrial complex was followed by a His potential The A H interval was normal average values for 10 beats equaling 87 msec (normal range = 54 to 130 msec) The H Q interval of conducted beats was markedly prolonged average for ten beats equaling 190 msec (normal range = 31 to 55 msec) Non conducted P waves were followed by an H potential but not by a QRS Thus the site of A V block was distal to the His recording site This together with findings of trifascicular block on surface ECG s was suggestive of bilateral bundle branch involvement

Hemodynamic studies Left and right heart catheterization were carried out on January 16 and January 17 1976 Hemodynamic measurements were made both during spontaneous beating during which the patient exhibited variable degrees of A V block with an average ventricular rate of 29 to 40 beats/minute and during right ventricular pacing at rates of 75 to 90 beats/minute Findings are summarized in Table I Slightly increased left and right ventricular systolic pressures together with a small pulmonic systolic gradient which were present during sinus rhythm were normalized by pacing Cardiac index was normal at rest and increased slightly with pacing Systemic and pulmonary vascular resistances were normal Left ventricular aortic root and coronary angiography as well as ascorbic and shunt studies were all normal

Subsequent course A permanent demand pacemaker with an intrinsic firing rate of 85 beats/minute was implanted epicardially on January 25 1976 Since that time the patient's symptoms have disappeared heart size has normalized and he has returned to full activity

Discussion

The case of a young otherwise healthy male who presented with symptomatic trifascicular block at age 21 is described The clinical setting including the absence of other stigmata of heart disease the rapid progression of symptoms and of the conduction disturbance and the negative family history when taken together with electrocardiographic evidence of bilateral bundle branch disease conform with criteria suggested for the antemortem diagnosis of Lenegre s disease[1,5,11] His bundle electrograms showing an infranodal

uation including echocardiograms and cardiac catheterization were unremarkable. Progression of bilateral bundle branch disease in a young patient without other demonstrable heart lesions and a negative family background conforms with criteria for Lenegre's disease. To our knowledge this represents the youngest reported patient with this entity. Possible electrophysiologic basis of block and of exercise induced improvement in A-V conduction also are considered.

The authors wish to express their appreciation to Mr. Jerry Bonnar for his technical assistance.

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represents a principal action of catechol amines[27,30] Improvement in A V conduction in the face of the increase in sinus rate is more difficult to explain since the catecholamines do not normally influence conduction to any significant degree[7,30]

Findings from glass microelectrode studies that specimens of diseased human heart muscle contain large numbers of partially depolarized fibers,[28,31,32] that is fibers with less negative than normal levels of diastolic potential, may be pertinent Given the known voltage dependance of conduction,[13,36] this would be expected to predispose to slow and decremental conduction and local block[33,36] Excitability and conduction were, in fact frequently depressed in such specimens and varying degrees of block were commonplace In addition, action potential duration and refractoriness were generally prolonged[3] It is also pertinent that partially depolarized fibers may differ both qualitatively and quantitatively with respect to their response to a number of important cardioactive drugs and ions as compared with normal cells[31] Catecholamines are best known in this regard[25,30,35] As noted above, their principal action on normal heart muscle is to enhance pacemaker activity Direct effects on conduction and refractoriness are minimal In partially depolarized fibers on the other hand, these agents act to restore membrane potential towards normal, with corresponding improvement in voltage dependant conduction disturbances[8,30,35] The limited nature of the changes in electrical activity which can occur in response to cellular injury and disease suggests that block and increased refractoriness in patients with Lenegre s disease may be due to the presence of partially depolarized fibers in the bundle branch system To the extent that this holds exercise induced improvement in conduction would be most readily explicable in terms of the hyperpolarizing action of the catecholamines

Our patient resembles the other reported instance of Lenegre s disease in a young adult[4] in that both were males and both presented initially with documented conduction system disease at 21 years of age The two cases differ in that the patient reported by Dhingra and colleagues[4] presented with left bundle branch block an entity which has been described as a relatively benign entity in the young[37] Conduction system disease progressed very slowly with intermittent 2 1 and more advanced degrees of A V block making their first appearance at age 31 There was no significant progression up to the time of pacemaker implantation at age 40 The patient remained asymptomatic throughout, due at least in part, to the fact that he continued to be able to generate an idioventricular escape rhythm at a tolerable rate (35/minute) during periods of advanced block In contrast, our patient presented with left anterior divisional block and right bundle branch block a combination which serves as the forerunner of complete heart block in 40 to 59 per cent of cases[8,9] Conduction system involvement progressed rapidly with development of incomplete trifascicular block and 2 1 and advanced A V block over an eight month period accompanied by increasingly severe and incapacitating dizziness fatigue and shortness of breath necessitating pacemaker implantation at age 22 Failure of idioventricular escape rhythms to appear during periods of A V block provides additional evidence for the much greater extent of the disease process

The striking differences in extent of conduction system involvement and in rate of progression of the disease process between the two patients underscore the diversity of the disease process and the need for careful follow up It also emphasizes the importance of achieving an improved understanding of the natural history of the disease Finally, failure to find evidence of second degree A V block in multiple, random standard electrocardiograms at a time when twelve hour Holter monitoring records revealed numerous such episodes supports contentions[19] concerning the importance of prolonged rhythm monitoring as part of the evaluation process

Summary

The case of a 22 year old white male without known heart disease who presented with activity related lightheadedness at age 19 and dizziness and fatigue at age 21 is described Standard electrocardiograms (ECG s) revealed intermittent complete trifascicular block Rapid progression of symptoms over the succeeding eight months resulted in increasing incapacity Holter monitoring demonstrated that symptoms were related to development of second and higher degrees of A V block Normal A H interval and markedly prolonged H Q interval on His bundle electrograms indicated that block was infranodal and localized to bundle branch system Conduction problems aside clinical and laboratory eval

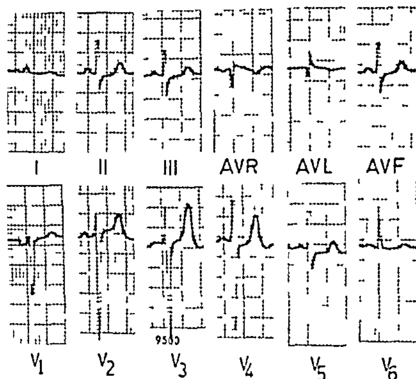


Fig 1 The ECG strip shows high lateral myocardial ischemia. The T wave in Lead III is higher than the T wave in Lead I



Fig 2 An area of myocardium revealing typical fresh myocardial infarction changes. (Magnification ×100 hematoxylin and eosin)

Myocardial infarction associated with the Riley-Day syndrome

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Familial dysautonomia is a clinical entity, first described by Riley Day and colleagues in 1949[1]

The disease is primarily limited to Ashkenazy Jews and is genetically transmitted as an auto somal recessive trait The syndrome is character ized by episodic hypertension cyclical vomiting feeding difficulties dysphagia and aspiration failure to thrive alacrimia excessive sweating diminished pain sensation breath holding at tacks, absence of the fungiform papillae of the tongue characteristic facies and scoliosis[1 4]

The basic defect is probably in the production or release of the catecholamines[2] These patients show exaggerated responses to adrenergic and cholinergic agents This was interpreted as hypersensitivity related to a partial autonomic denervation[4]

The patients rarely survive beyond the third decade of their life[2] The usual causes of death are recurrent pneumonia as a result of their swallow ing defect subarachnoid hemorrhage uremia or unexplained sudden death[1]

Myocardial infarction as a cause of death in Riley Day syndrome has not been documented previously The purpose of this communication is to report such an association and to discuss its interesting possible pathogenetic mechanisms, which may be linked to the fundamental defect of the disease

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Case report

A 23 year old Ashkenazy Jew was admitted to the medical department after a convulsive episode and loss of consciou ness for several minutes

He was previously diagnosed as suffering from familial dysautonomia according to

1 Difficulties in feeding from birth and a general failure to thrive
2 Absence of fungiform papillae of tongue and impaired taste sensation
3 Excessive perspiration especially while eating
4 Failure to shed tears when crying
5 Relative indifference to pain (as venipuncture)
6 Episodic crises of vomiting hypertension and fever
7 Absent deep tendon reflexes
8 Slurred monotonous dysarthric speech
9 Orthostatic hypotension
10 Metacholine hypersensitivity

Physical examination on admission revealed a pale malde veloped male with facial asymmetry and kyphoscoliosis His blood pressure was 280/170 and the pulse 130 beats per minute His cervical veins were engorged A third heart sound could be heard There were bilateral basal pulmonary crepita tions and a tender liver could be palpated 2 cm below the costal margin Pitting edema of the legs was noted

Fundoscopic examination revealed a fourth degree hyper tensive retinopathy and bilateral basal papilledema

A neurologic examination revealed no abnormal findings. An ECG strip recorded sinus tachycardia and high lateral wall myocardial ischemia (Fig 1)

Pertinent laboratory findings were hemoglobin concentra tion was 9 3 Gm per cent the WBC count was 6 800 with a normal differential the BUN was 78 mg per cent and the creatinine 7 3 mg per cent the SGOT was 62 i u and the SGPT 40 i u calcium level was 9 1 mg per cent and the phosphorous level was 5 8 mg per cent bilirubin level was 1 2 mg per cent of which 0 3 mg per cent was direct His urine contained daily protein excretions of 1 8 Gm

The patient was cooperative had no complaints except for mild dyspnea and denied suffering any chest pain His blood pressure fluctuated between 20 180 and 170 80

The patient was confined to bed and hydralazine HCl chlorpromazine HCl digoxin, and furosemide were administered. His general condition improved Dynamic changes were not observed in repeated ECG recordings and no further elevation of the transaminases was noted On the third day of hospitalization the patient was found dead in his bed

At autopsy the heart weighed 3 5 Gm There was a markedly hypertrophic left ventricular myocardial wall showing fresh myocardial infarction (Fig 2) involving septal posterior and lateral wall as well as the papillary muscle White scars situated mainly in the papillary muscle were the expression of previous infarctions (Fig 3) The coronary arteries showed advanced atherosclerotic changes in all branches The microscopic examination of the infarcted myocardium revealed changes consistent with myofibrillar degeneration (Fig 4)

It seems that a major arrhythmia was responsible for the sudden death of our patient

Discussion

This patient s case history fulfills the criteria proposed by Riley and associates for familial dysautonomia The association of the entity with myocardial infarction deserves some explanations as to the possible pathogenetic mechanisms involved

A sudden discharge of epinephrine from the adrenals which contain normal or increased amounts of catecholamines in patients with familial dysautonomia was postulated to explain their crises of hypertension tachycardia and fever but this mechanism is not universally accepted

Since the myocardial myofibrillar degeneration demonstrated in our patient was similar to that of the catecholamine cardiomyopathy reported to result after systemic administration of catecholamines or direct application of adrenalin to myocardial fibers we favor the assumption that a sudden catecholamine discharge" is responsible for the hypertensive crisis observed as well as for part of the myocardial damage

Patients with the Riley Day syndrome have denervation hypersensitivity expressed as exaggerated response to sympathomimetics and such a sudden epinephrine discharge is followed by profound vasoconstriction

As a result in our patient the elevated blood pressure (280/170) and tachycardia (130 beats per minute) were responsible for an increased myocardial oxygen demand which probably unsupplied by the prematurely atherosclerotic coronary vessels initiated an ischemic myocardial process

Two additional mechanisms could theoretically aggravate the myocardial injury

1 Sympathomimetic drugs may induce a selective intracardiac diversion of blood away from the subendocardium toward the epicardium causing subendocardial ischemia or even frank subendocardial infarction A similar mechanism initiated by a sudden epinephrine discharge from the adrenals could account for the subendocardially localized myocardial lesion found in our patient

2 Sympathetic substances may decrease the collateral flow to ischemic areas by dilatation of the coronary vessels a phenomenon given the name of coronary steal"

When suddenly exposed to high intrinsic epinephrine concentrations the coronary vessels of our patient possibly diverted the blood flow away from the well developed myocardial collateral system augmenting the ischemic process

It seems surprising that no previous cardiac damage was reported in patients with familial dysautonomia in spite of the potential mechanisms that may induce it However it is not to be ruled out that a major arrhythmia or myocardial infarction were responsible for part of the sudden death cases recorded in these patients

Summary

The sudden death of a 23 year old Ashkenazi Jew suffering from familial dysautonomia was probably caused by an arrhythmia accompanying a myocardial infarction Such a report is unique

Diffuse coronary atherosclerosis and direct myocardial catecholamine cardiomyopathy seem responsible for the myocardial damage However diversion of the endocardial blood flow toward epicardium and a coronary steal phenomenon both the result of a sudden catecholamine discharge could aggravate the ischemic injury

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Fig 3 Patchy fibrous scarring of myocardium depicting an old myocardial infarct (Magnification ×100 hematoxylin and eosin)



Fig 4 An area of myocardial fibers showing classical myofibrillar degenerative changes with transverse bands and intervening granularity such as noted after prolonged catecholamine stimulation (Magnification ×400 Masson s trichrome stain)

The patient was cooperative, had no complaints except for mild dyspnea and denied suffering any chest pain. His blood pressure fluctuated between 280/150 and 170/60.

The patient was confined to bed and hydralazine HCl, chlorpromazine HCl, digoxin and furosemide were administered. His general condition improved. Dynamic changes were not observed in repeated ECG recordings and no further elevation of the transaminases was noted. On the third day of hospitalization the patient was found dead in his bed.

At autopsy the heart weighed 3 .. Gm. There was a markedly hypertrophic left ventricular myocardial wall showing fresh myocardial infarction (Fig. 2) involving septal, posterior and lateral wall as well as the papillary muscle. White scars situated mainly in the papillary muscle were the expression of previous infarctions (Fig. 3). The coronary arteries showed advanced atherosclerotic changes in all branches. The microscopic examination of the infarcted myocardium revealed changes consistent with myofibrillar degeneration (Fig. 4).

It seems that a major arrhythmia was responsible for the sudden death of our patient.

Discussion

This patient's case history fulfills the criteria proposed by Riley and associates for familial dysautonomia.[1] The association of this entity with myocardial infarction deserves some explanations as to the possible pathogenetic mechanisms involved.

A sudden discharge of epinephrine from the adrenals[4] which contain normal or increased amounts of catecholamines in patients with familial dysautonomia was postulated to explain their crises of hypertension, tachycardia and fever, but this mechanism is not universally accepted.

Since the myocardial myofibrillar degeneration demonstrated in our patient was similar to that of the catecholamine cardiomyopathy reported to result after systemic administration of catecholamines or direct application of adrenalin to myocardial fibers, we favor the assumption that a sudden catecholamine discharge is responsible for the hypertensive crisis observed as well as for part of the myocardial damage.

Patients with the Riley Day syndrome have denervation hypersensitivity expressed as exaggerated response to sympathomimetics and such a sudden epinephrine discharge is followed by profound vasoconstriction.

As a result, in our patient the elevated blood pressure (280/170) and tachycardia (130 beats per minute) were responsible for an increased myocardial oxygen demand which probably unsupplied by the prematurely atherosclerotic coronary vessels initiated an ischemic myocardial process.

Two additional mechanisms could theoretically aggravate the myocardial injury.

1. Sympathomimetic drugs may induce a selective intracardiac diversion of blood away from the subendocardium toward the epicardium, causing subendocardial ischemia or even frank subendocardial infarction. A similar mechanism initiated by a sudden epinephrine discharge from the adrenals could account for the subendocardially localized myocardial lesion found in our patient.

2. Sympathetic substances may decrease the collateral flow to ischemic areas by dilatation of the coronary vessels, a phenomenon given the name of coronary steal.

When suddenly exposed to high intrinsic epinephrine concentrations, the coronary vessels of our patient possibly diverted the blood flow away from the well developed myocardial collateral system, augmenting the ischemic process.

It seems surprising that no previous cardiac damage was reported in patients with familial dysautonomia in spite of the potential mechanisms that may induce it. However, it is not to be ruled out that a major arrhythmia or myocardial infarction were responsible for part of the sudden death cases recorded in these patients.

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The sudden death of a 23 year old Ashkenazy Jew suffering from familial dysautonomia was probably caused by an arrhythmia accompanying a myocardial infarction. Such a report is unique.

Diffuse coronary atherosclerosis and direct myocardial catecholamine cardiomyopathy seem responsible for the myocardial damage. However, diversion of the endocardial blood flow toward epicardium and a coronary steal phenomenon, both the result of a sudden catecholamine discharge, could aggravate the ischemic injury.

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Clinical pathologic conference*

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Clinical history

A 71 year old white female retired school teacher was admitted to a local hospital because of extreme fatigue anorexia nausea hiccoughs flatulence and constipation of duration of two years One year prior to admission she was hospitalized because of an episode of acute exertional dyspnea She was found to have paroxysmal atrial fibrillation and left ventricular failure attributed to arteriosclerotic heart disease Treatment with digitalis and diuretics resulted in reversion to a normal sinus rhythm Gastrointestinal symptoms persisted and she began to lose weight Just prior to her admission to the hospital she experienced increasing fatigue and two episodes of acute epigastric discomfort associated with nausea fullness belching epigastric burning and constipation

In childhood she had had rheumatic fever and migraine headaches In recent years her headaches had recurred but she noted they were usually associated with tension and anxiety In 1918 she had had malaria and was treated with Atabrine

Physical examination The temperature was 98 F the blood pressure 138/80 (?) and pulse 80 and irregular The patient was a rather poorly nourished elderly woman lying quietly in bed in no acute distress There was no evidence of jaundice cyanosis or pallor Examination of the optic fundi revealed Grade II arteriosclerotic changes Mucous membranes of the mouth were of good color and the tongue was normal and showed normal papillation The neck veins were not distended There was no significant peripheral lymph node enlargement The chest was symmetrical The lungs were clear to percussion but there were a few moist rales on auscultation of both bases The cardiac apical impulse was 1 cm outside the midclavicular line in the fifth inter space The rhythm was grossly irregular no murmurs or thrills were detected Peripheral pulses were adequate bilaterally Neurological examination was within normal limits Pelvic and rectal examinations were normal except for the presence of an atrophic vaginitis

Laboratory data The hemoglobin was 11 4 Gm per cent Red blood count (RBC) indices were as follows mean corpuscular volume (MCV) 90 mean corpuscular hemoglobin concentration (MCHC) 34 mean corpuscular hemoglobin (MCH) 30 The reticulocyte count was 3 6 per cent A urinalysis was normal The blood urea nitrogen (BUN) was 30 mg per cent and fasting blood sugar 108 mg per cent The alkaline phosphatase was 3 8 mU per ml The total protein was 6 8 Gm per cent with albumin 3 7 Gm per cent A serum protein electrophoretic pattern (Fig 1) revealed a monoclonal spike in the gamma globulin region constituting 26 per cent of the total protein The serum sodium was 125 mEq per liter potassium 4 7 mEq per liter chloride 89 mEq per liter and CO_2 25 mEq per liter A repeat serum glutamic oxaloacetic transaminase (SGOT) was 110 mU per ml The serum lactic dehydrogenase was 1180 mU per ml and creatine phosphokinase was 127 mU per ml Tubeless gastric analysis showed presumptive evidence of achlorhydria and gastric analysis done with studies of the gastric washings was negative for free acid on three successive days

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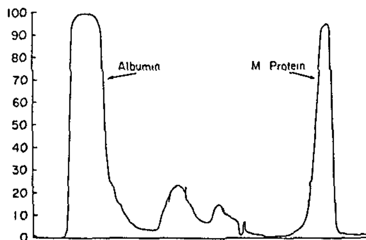


Fig 1 Serum protein electrophoresis The monoclonal pattern is apparent

An electrocardiogram (Fig 2) showed atrial fibrillation and frequent premature ventricular contractions with non specific ST and T wave changes Q waves in leads AV_f and in V_1 through V_4 were thought to be probable residuals of an old anterior myocardial infarction

Chest x rays showed minimal bilateral pleural effusions and probable slight cardiac enlargement A cholecystogram was negative An upper gastrointestinal series showed a filling defect in the lesser curvature of the stomach A barium enema was normal Skeletal surveys were negative A liver scan was reported as showing a liver slightly increased in size with apparent replacement of normal liver tissue in the left lobe of the liver consistent with metastatic disease Gastroscopic examination was performed under local anesthesia and was reported to show a large reddened soft raised lesion on the lesser curvature of the upper body of the stomach which was demarcated from the normal mucosa at its edges A bone marrow aspiration was performed which showed a normally cellular marrow Erythropoiesis was normoblastic and slightly reduced in quantity There was normal maturation of the myeloid cells and a slight but definite increase in the number of plasma cells in the bone marrow with occasional binucleated plasma cells

Her course in the hospital was essentially uneventful except that she continued to complain of the same gastrointestinal symptoms that had brought her to the hospital On Sept 28 1968 at 12 30 P M , she experienced an acute episode of dyspnea, cyanosis and cough at which time there was neck vein distention, the pulse was 114 and there were numerous moist rales throughout both lung fields A diagnosis of acute pulmonary edema was made but x ray findings were suggestive of an early bronchopneumonia in the right mid lung field She was treated vigorously with additional digitalis, diuretics, antibiotics and received nasal oxygen She appeared to be improving but died suddenly on Oct 4 1968 at 11 00 P M

Clinical discussion

DR FRANKLIN MULLINAX This 71 year old female was sick for two years with progressive gastrointestinal symptoms which led to her hospitalization A year before admission she had an episode of paroxysmal atrial fibrillation On examination she presented with atrial fibrillation a large heart, and a large liver While the work up was progressing she experienced an acute cardiopulmonary episode, apparently a pulmonary embolus Six days later she died suddenly

Studies during hospitalization revealed the following a monoclonal (M) spike on serum protein electrophoresis a stomach lesion, a large heart and an abnormal electrocardiogram In addition, she had achlorhydria and macrocytosis May we see the x rays?

DR WILLIAM WEIDNER This patient was admitted to a local hospital The work up included a chest x ray a skeletal survey and examinations of her colon stomach and small bowel

The chest x ray reveals generalized cardiac enlargement Despite the history of rheumatic fever there is no evidence of specific enlargement of any of the chambers The left atrium is not dilated There is a slight bulge of left auricular appendage but certainly not enough to diagnose valvular heart disease There is some fluid at the left base and slight perivascular cuffing of the vessels So there is minimal pulmonary edema and congestive failure There are no lesions in the bone

A barium enema shows the colon to be rather redundant but otherwise normal and a post evacuation film reveals normal mucosal pattern The terminal ileum is normal The gallbladder visualized normally Again the bones appear normal

This film of her upper gastrointestinal tract reveals definitely abnormal mucosal folds on the lesser curvature of the stomach and a lesion which involves at least that much of the stomach The remainder of the mucosal pattern of her

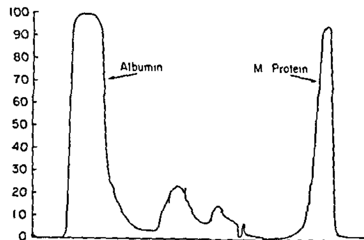


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Table I Dıagnostıc classıficatıons ın 400 cases of monoclonal gamma globulın abnormalıtıes[1]

Dıagnosıs	*No of cases*
Multıple myeloma (ıncludıng amyloıdosıs)	262
H chaın (Franklın s) dısease	3
Waldenstrom s macroglobulınemıa	41
Lymphoma	23
Monoclonal gammopathy wıth associated neoplasm	31
Monoclonal gammopathy without associated neoplasm	40
	400

The term *M spıke* ındıcates monoclonal spıke It ıs a very good term because of ıts theoretıc basıs and practıcal sıgnıficance Theoretıcally, we envı sıon that an ındıvıdual normally has many popu latıons or clones of plasma cells and that each clone produces ıts partıcular type of ımmunoglob ulın that ıs, antıbody If there ıs a general overprolıferatıon of plasma cells a general ıncrease ın serum gamma globulın ıs seen If only one clone of plasma cells prolıferates a homogen eous proteın ıs produced wıth a resultant dıscrete elevatıon, the M spıke on the electrophoretıc pattern Practıcally, the findıng of an M spıke ıs usually very sıgnıficant dıagnostıcally It ındı cates that there ıs an abnormal prolıferatıon of one clone of plasma cells as occurs, for example ın multıple myeloma We may revıew the course of multıple myeloma to see ıf thıs ıs the dıagnosıs ın the present case

The patıent wıth myelomatosıs may present wıth bone paın or the dıagnosıs may be suggested by clınıcal happenıngs such as repeated pneumo nıas, occurrence of anemıa or renal dısease Often the dıagnosıs ıs quıetly suggested by a laboratory findıng proteınurıa hyperglobulınemıa marked elevatıon of the erythrocyte sedımentatıon rate or hypercalcemıa Occasıonally, the proteın ıtself ıs responsıble for clınıcal problems such as hyper vıscosıty, hyperlıpıdemıa, or coagulatıon abnor malıtıes

The most characterıstıc and troublesome symptom ıs bone paın The paın starts ınsıdı ously wıth vague musculoskeletal complaınts whıch progress over the course of months to become more constant and less neurotıc as they clearly become related to motıon coughıng pres sure Then constant neurıtıc paın may evolve wıth acute exacerbatıons assocıated wıth patho logıc fractures The skeletal ınvolvement of myelomatosıs ıs unusual ın beıng largely lımıted to myeloıd contaınıng bone so that pathologıc fractures occur more centrally than ıs usual for trauma

The dıagnosıs of multıple myeloma ıs made by the findıng of approprıate ımmunoglobulın changes ın serum and/or urıne, tıssue plasmacy tosıs, and a compatıble clınıcal pıcture Lackıng bone lesıons, thıs patıent dıd not present the approprıate clınıcal pıcture and we should there fore consıder other condıtıons assocıated wıth an M spıke on serum proteın electrophoresıs

The clınıcal dıagnoses ın 400 cases of mono clonal gammopathy revıewed by Osserman and Takatsukı[1] are presented ın Table I* Multıple myeloma occurred ın two thırds of the patıents Amyloıdosıs, whıch was the domınant or an asso cıated manıfestatıon ın 8 per cent of these patıents wıth multıple myeloma was not lısted as a separate classıficatıon I shall return to amyloı dosıs H chaın (Franklın s) dısease ıs a rare plasma cell dyscrasıa whıch need not be dıscussed today Dıscussıon of Waldenstrom's macroglobu lınemıa ıs also ınapproprıate today Patıents wıth lymphomas such as lymphosarcoma, chronıc lymphocyte leukemıa or Hodgkın s dısease may have a serum proteın M spıke, a poınt to be consıdered when the stomach lesıon ın thıs case ıs consıdered Another group of patıents here 7 per cent, have M spıkes of cause unknown wıth an assocıate non plasma cell neoplasm Of course some of the cancers ınvolve the gastroıntestınal tract The assocıatıon may be a sımple concur rence of problems However, the findıng of plasma cells around the perıphery of tumors and the rare dısappearance of the M proteın after tumor removal suggest that the plasma cell prolıferatıon ıs a response to the tumor

Fınally, there ıs a group of cases havıng mono clonal gammopathy wıthout assocıate neoplasm benıgn monoclonal gammopathy In these pa tıents the electrophoretıcally homogeneous band or spıke ıs generally small (less than 1 Gm per cent) and remaıns unchanged for several years Serum proteın electrophoretıc studıes are appar ently a way of lıfe ın Sweden where large popula tıons have been studıed[4] One per cent of the adult populatıon and 6 per cent of those over age 80 harbor an M component Approxımately a

*Later dıscussıons of condıtıons assocıated wıth monoclonal ımmuno globulın patterns are found ın references 2 and 3

third of the elderly group have an associated cancer In the bone marrows of this largely normal population with monoclonal serum protein patterns the plasma cell percentage varied from 1 to 20 Most had less than 3 per cent plasma cells Although it is possible that the present patient had benign monoclonal gammopathy the rather prominent electrophoretic spike (1 8 Gm per cent) and associated clinical problems suggest other explanations

The discussion of M spikes in patients with associated tumors leads to the second problem the stomach lesion Ninety five per cent of stomach tumors are adenocarcinomas. This patient s tumor did not produce a typical linitis plastica with diffuse invasion Instead peristaltic waves progressed nicely right up to the lesion A lymphoma would more likely produce this rather isolated lesion I wondered whether this might be a plasmacytoma of the stomach Such tumors may occur but they are rare and would not explain other features in the present case At this stage of analysis one might suggest that the patient had monoclonal gammopathy associated with a stomach cancer while retaining the thought that the x ray suggests a tumor other than adenocarcinoma

The third problem heart disease is at first glance straightforward A 71 year old woman with arteriosclerosis and an old myocardial infarction experienced progressive congestive heart failure perhaps worsened by another silent myocardial infarction But she never had pain The bout of auricular fibrillation a year before her terminal admission may have been related to her terminal illness rather than an isolated event in the past The electrocardiogram is not diagnostic of arteriosclerotic coronary artery disease An electrocardiogram reflects electrical events in the heart and this one shows low voltage and a loss of anterior forces Any lesion destroying an appropriate amount of muscle would produce these changes In the present context the obvious possibility is amyloidosis

Amyloid heart disease presents in one of three ways First there may be insidious progression of congestive heart failure Second the disease may present with arrhythmias or conduction disturbances Third and rare is the occurrence of typical clinical coronary artery disease attributable to amyloid infiltration of the coronary vessels

Some general comments about amyloid are in order Whereas conventional light microscopic studies give the impression that amyloid is an amorphous non specific deposit studies with the electron microscope show clearly that amyloid is or contains a characteristic fibrillar protein that is not collagen Amyloid is occasionally seen inside plasma cells This finding suggests a possible direct relationship to plasma cell dyscrasias and gives support to Osserman s inclusion of amyloidosis as part of the myelomatosis spectrum

Clinically it is useful to classify amyloidosis as either primary secondary or myeloma associated Primary amyloidosis particularly affects the heart tongue tendon sheaths and nerves and somewhat less so the liver spleen and kidneys which are more likely targets in the amyloidosis secondary to rheumatoid arthritis leprosy Hodgkin s disease infected decubiti and a variety of other inflammatory conditions Clinically and pathologically there is however a great overlap in the presentation and course of primary and secondary amyloidosis It is not yet clear whether primary amyloidosis is essentially a form of multiple myeloma Broadly the course of multiple myeloma is dominated by destructive invasive masses of plasma cells whereas the course of primary amyloidosis is determined by the sites of amyloid deposition Case of "myelomatosis with associated amyloid have clinical features of both plasma cell proliferation and amyloid deposition

The clinical course of primary amyloidosis is quite variable being dependent on the sites and extent of amyloid deposition The adrenal glands may be involved conceivably being reflected in this case by the low serum sodium although I suspect that this is part of the electrolyte disturbance of congestive heart failure The pancreas may be infiltrated Approximately 80 per cent of diabetic patients over the age of 50 have amyloid in the pancreas as contrasted with less than 15 per cent of non diabetics In the case today there was hyperglycemia which may reflect pancreatic amyloidosis

Another site of amyloid deposition is the gastrointestinal tract from the tongue to the rectum Amyloidosis of the stomach may be so extensive that achlorhydria occurs and a stomach tumor is mimicked One distinguishing character

Recent studies cl arly show that at least some amylo is contain fragments of immunogl bulin light chains.

Table I Diagnostic classifications in 400 cases of monoclonal gamma globulin abnormalities[1]

Diagnosis	*No of cases*
Multiple myeloma (including amyloidosis)	262
H' ² chain (Franklin s) disease	3
Waldenstrom s macroglobulinemia	41
Lymphoma	23
Monoclonal gammopathy with associated neoplasm	31
Monoclonal gammopathy without associated neoplasm	40
	400

The term *M spike* indicates monoclonal spike It is a very good term because of its theoretic basis and practical significance Theoretically, we envision that an individual normally has many populations or clones of plasma cells and that each clone produces its particular type of immunoglobulin that is, antibody If there is a general overproliferation of plasma cells a general increase in serum gamma globulin is seen If only one clone of plasma cells proliferates a homogeneous protein is produced with a resultant discrete elevation the M spike on the electrophoretic pattern Practically, the finding of an M spike is usually very significant diagnostically It indicates that there is an abnormal proliferation of one clone of plasma cells as occurs, for example in multiple myeloma We may review the course of multiple myeloma to see if this is the diagnosis in the present case

The patient with myelomatosis may present with bone pain or the diagnosis may be suggested by clinical happenings such as repeated pneumonias, occurrence of anemia, or renal disease Often the diagnosis is quietly suggested by a laboratory finding proteinuria, hyperglobulinemia marked elevation of the erythrocyte sedimentation rate or hypercalcemia Occasionally the protein itself is responsible for clinical problems such as hyperviscosity, hyperlipidemia or coagulation abnormalities

The most characteristic and troublesome symptom is bone pain The pain starts insidiously with vague musculoskeletal complaints which progress over the course of months to become more constant and less neurotic as they clearly become related to motion coughing pressure Then constant neuritic pain may evolve with acute exacerbations associated with pathologic fractures The skeletal involvement of myelomatosis is unusual in being largely limited to myeloid containing bone so that pathologic fractures occur more centrally than is usual for trauma

The diagnosis of multiple myeloma is made by the finding of appropriate immunoglobulin changes in serum and/or urine, tissue plasmacytosis, and a compatible clinical picture Lacking bone lesions, this patient did not present the appropriate clinical picture and we should therefore consider other conditions associated with an M spike on serum protein electrophoresis

The clinical diagnoses in 400 cases of monoclonal gammopathy reviewed by Osserman and Takatsuki[1] are presented in Table I * Multiple myeloma occurred in two thirds of the patients Amyloidosis, which was the dominant or an associated manifestation in 8 per cent of these patients with multiple myeloma was not listed as a separate classification I shall return to amyloidosis H chain (Franklin s) disease is a rare plasma cell dyscrasia which need not be discussed today Discussion of Waldenstrom s macroglobulinemia is also inappropriate today Patients with lymphomas, such as lymphosarcoma, chronic lymphocyte leukemia or Hodgkin s disease may have a serum protein M spike, a point to be considered when the stomach lesion in this case is considered Another group of patients, here 7 per cent have M spikes of cause unknown with an associate non plasma cell neoplasm Of course some of the cancers involve the gastrointestinal tract The association may be a simple concurrence of problems However, the finding of plasma cells around the periphery of tumors and the rare disappearance of the M protein after tumor removal suggest that the plasma cell proliferation is a response to the tumor

Finally there is a group of cases having monoclonal gammopathy without associate neoplasm *benign monoclonal gammopathy* In these patients the electrophoretically homogeneous band or spike is generally small (less than 1 Gm per cent) and remains unchanged for several years Serum protein electrophoretic studies are apparently a way of life in Sweden where large populations have been studied[4,5] One per cent of the adult population and 6 per cent of those over age 80 harbor an M component Approximately a

* Later discussions of conditions associated with monoclonal immunoglobulin patterns are found in references 2 and 3



Fig 4 Ca tric lesion demon trating gross thickening of blood vessel wall by amyl id deposits.

In summary my analysis is as follows First the monoclonal pattern on serum protein electro phoresis commands attention In absence of clear bone invasion typical multiple myeloma cannot be diagnosed and other causes of plasma cell dyscrasia must be considered Second the unusual stomach tumor together with other features of the case suggests gastrointestinal involvement with amyloid Third and perhaps most helpful diagnostically is the heart disease In an older person with heart disease no history of chest pain and an electrocardiogram revealing low voltage conduction defects or a pattern suggesting myocardial infarction the possibility of primary amyloidosis should spring immediately to mind with confirmation by biopsy usually of the rectal mucosa being sought immediately

Clearly I cannot be sure what the patient had But clearly she should have had amyloidosis

Pathologist s Discussion

DR RALPH BECK The clinical diagnosis of amyloidosis involving multiple organs and asso ciated with a plasma cell dyscrasia is in complete accord with the pathological findings It will also be seen that distribution of the amyloid deposits imposes no strain on clinicopathologic correla tion As the major anatomical diagnosis has been stated I shall now present the further findings at necropsy and conclude with comments on the classification of amyloidosis

At autopsy the body was that of a poorly nourished elderly woman She was 64 inches tall and weighed 100 pounds In describing more specific aspects of the necropsy it may be perti nent to begin with the bones The absence of radiologic evidence of lytic lesions is helpful for two reasons First as discussed by Dr Mullinax this is an important negative finding in analysis of a case of plasma cell dyscrasia Second the pathologist is practically limited in the complete ness of his examinations of bone Sections of bone marrow did however show increased numbers of plasma cells which were morphologically normal apart from a few binucleated forms

The heart weight of 430 Gm., when related to the patient s sex and stature represents an impressive degree of cardiomegaly which affected all chambers There was diffuse fibrosis of the left ventricular septum The major coronary arteries were patent and gross changes were limited to mild non occlusive atherosclerosis of the anterior descending branch of the left coronary artery There were no signs of recent infarction but several minute inconspicuous gray nodules were present in the myocardium

Histologically several pathological features are observed (Fig 3) Hypertrophy is confirmed by the large diameter of many myocardial cells There is increase in interstitial connective tissue The most striking abnormality is seen in the walls of the intramural coronary arteries and arterioles

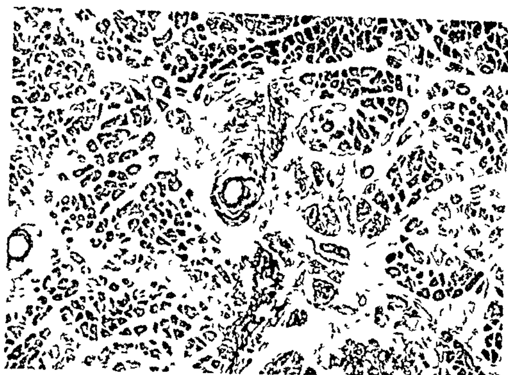


Fig 3A Myocardial tissue demonstrating hypertrophy of myocardial cells and thickening of intramural arteries and arterioles by amyloid (Hemotoxylin and eosin stain Original magnification ×100)

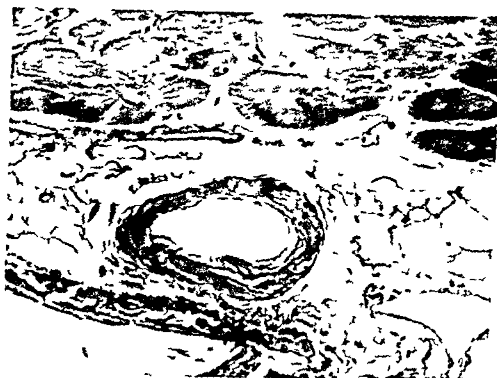


Fig 3B Higher magnification of same structures 287X as in Fig 3A (Original magnification ×287)

istic is the discrete lesion surrounded by normal stomach It is then reasonable to suggest that this patient had an uncommon form of stomach tumor amyloid

Finally, there are the clinical events during her hospitalization The episode of dyspnea and occurrence of a lung lesion are in keeping with the diagnosis of pulmonary embolus and infarction which was then treated vigorously The amyloid laden heart is inordinately sensitive to digitalis induced arrhythmias Rather than invoking anything else catastrophic at the end of the illness I suggest that she died because of a cardiac arrhythmia

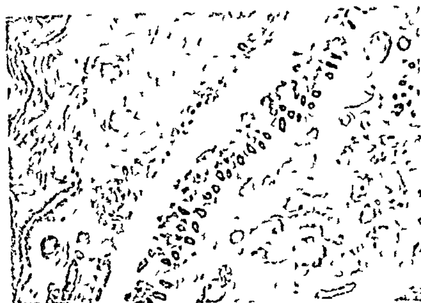


Fig 4 Gastric lesion demonstrating gross thickening of blood vessel wall by amyloid deposits

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which contain a deposit of diffuse homogenous eosinophilic material Medial and intimal detail is obscured while reduction in lumen diameter ranges from slight narrowing to subtotal occlusion Congo red staining and green birefringence with polarized light identifies the material as amyloid No discrete amyloid deposits were seen in the heart muscle but several foci of myofibrillary degeneration were present, presumably secondary to ischemia due to the intramural vascular disease

A filling defect in the stomach attracted interest and speculation In the lesser curvature of the stomach there was a 3 5 cm elevated area of hyperemic mucosa Histologically (Fig 4) this conforms closely with the radiological interpretation of a submucosal lesion with intact mucosa The mucosal elevation and thickening of the submucosa is related mainly to amyloidosis of the blood vessels which are greatly thickened, but additionally discrete nodules of amyloid are also present Essentially similar vascular changes were present in the lungs kidney, spleen adrenals liver and lymph nodes The pancreas is chiefly remarkable for the extent of vascular lesions and confluent deposits which obliterate about 30 per cent of endocrine and exocrine tissue

Two other findings conclude the catalog of lesions A pulmonary infarct of several days duration was present in the right mid lung Finally to make amends for the lack of surprise in the pathologic findings I can give a probable explanation for the liver scan which was interpreted as showing an abnormality in the left lobe, consistent with metastatic tumor In fact the area shows the condition known as peliosis hepatis a pathological curiosity composed of a congeries of endothelial channels in the sinusoids and between the parenchymal cells This lesion behaves like an angioma thwarting uptake of the isotope with resultant cold spots more usually indicative of necrosis or metastatic disease

With regard to classification of amyloidosis the traditional division has been into (1) primary amyloidosis (2) amyloidosis associated with *multiple myeloma* and (3) amyloidosis which may occur in patients with a variety of inflammatory diseases such as tuberculosis osteomyelitis rheumatoid arthritis, and *certain malignancies* Only marginal advance is made by *recognizing* that primary amyloid is more likely to involve the tongue and heart while secondary amyloid favors spleen kidneys, adrenal glands and liver These boundaries are too frequently transgressed to be of specific value particularly the amyloid associated with multiple myeloma which may share the distribution of both primary and secondary types Better prospects lie in investigating such basic questions as the properties and composition of amyloid and the pathogenetic mechanisms leading to its production

Letterer[1] in a succinct review traces to 1967 the development of research in amyloidosis Rokitansky referred to lardaceous liver in 1842 and two years later Christensen described and named a focal form of amyloidosis sago spleen The misnomer amyloid was coined by Virchow in 1853 who erroneously concluded on the basis of an iodine stain that the substance was related to starch or cellulose It is now appreciated that amyloid is largely or essentially composed of protein and that it possesses rather distinctive morphological and histologic properties

The affinity of amyloid for Congo Red stain its metachromasia with crystal violet stain and many other tinctorial characteristics continue to serve a useful purpose However, it is increasingly appreciated that these reactions are more variable and less specific than were once believed Other methods are of further help The apple green birefringence seen under polarizing lenses is a reliable indicator of the presence of amyloid while the fibrils with characteristic periodicity seen by electron microscopy are pathognomonic The similar electron microscopic picture given by amyloids of diverse *origin may* indicate that whatever the origin and pathogenesis of amyloidosis the final product is the same

Addendum

Since the presentation of this clinicopathologic conference there have been new findings concerning the chemistry and pathogenesis of amyloidosis They have been reviewed by Glenner and associates[11] Whether primary, secondary or myeloma associated amyloid is apparently a deposit of protein capable of forming anti parallel β pleated sheet configuration The amyloid of primary amyloidosis and myelomatosis may be derived from immunoglobulin light chains whereas amyloid secondary to chronic inflamma

tory diseases may be derived from a non immunoglobulin plasma protein also capable of giving rise to fibrils Further extensions of this work should lead to understanding of the various forms of amyloidosis

Final diagnosis Plasma cell dyscrasia with amyloidosis

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Fundamentals of clinical cardiology

Changes in saphenous veins used as aortocoronary bypass grafts

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The widespread use of reversed autogenous saphenous veins to bypass obstructed coronary arteries has stimulated interest in the long term morphologic and functional fate of the grafts Stenosis or complete occlusion of the graft is now recognized as an all too frequent complication of its use as an aortocoronary conduit [1 13] While all grafts develop some morphologic changes, the degree and the functional significance of the changes may be related to several factors including intraluminal pressure graft-wall ischemia thrombosis or fibrin deposition and repair of damaged endothelium and intima either from ischemia or trauma or both [11 14 3] This paper describes structural changes observed in saphenous veins used as aortocoronary conduits and discusses the relative contribution of the above factors to these changes

Normal saphenous vein

The normal human saphenous vein contains a thin *intima* consisting of relatively acellular fibrous tissue covered by a single layer of endothelial cells and separated from the media by a rudimentary internal elastic membrane (Fig 1) The *media* consists of multiple layers of smooth muscle cells separated by bundles of collagen ground substance and occasional short elastic fibers The majority of medial smooth muscle layers have a circular orientation, in areas near the venous valves however the middle circular layers have a more longitudinal arrangement Frequently, longitudinally oriented smooth muscle fasicles make up the innermost layers of the media The *adventitia* is composed of bundles of collagen with scattered fasicles of longitudinally oriented smooth muscle cells Broad loose bands of elastic fibers are present in abundance Vasa vasorum are present and may extend into the outermost portion of the media

Reported changes in saphenous vein grafts used as arterial conduits

Seven changes have been described in veins implanted in the arterial circulation [1] (1) endothelial damage (2) medial hypertrophy, (3) medial necrosis (4) graft-wall fibrosis (media and adventitia) (5) intimal fibrous thickening (6) intimal lipid deposition and (7) aneurysmal dilatation

In 1906 Carrel and Guthrie [4] described intimal thickening in veins implanted in dogs, and concluded that veins placed in the arterial circulation had a strong tendency to assume the character of an artery In further vein transplantation experiments in 1908 Carrel [5] described four characteristic changes in veins used as arteries in the *peripheral* circulation (1) intimal thickening (2) adventitial thickening (from fibrosis) (3) loss of the inner one third of the media and (4) loss of elasticity producing a fibrous tube *In addition* medial hypertrophy was observed in some grafts The development of vascular surgery utilizing saphenous veins for femoropopliteal bypass and aortocoronary bypass brought renewed interest in the long term fate of these grafts

In early studies of the use of veins as conduits

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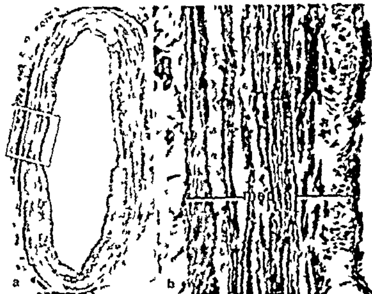


Fig. 1. Normal saphenous vein. *a*, Low power view showing medial circular and longitudinal smooth muscle layers. *b*, High power view of area enclosed in box in *a*. Multiple layers of circular smooth muscle separated by layers of fibrous tissue make up the media. Occasional longitudinal smooth muscle fascicles are present near the lumen. (Movat Stain; original magnification ×20 *(a)*, ×150 *(b)*.)

in the *aortocoronary* position. Dedomenico and associates described changes up to 2.5 years after implantation in canine jugular veins and in saphenous veins. A marked increase in both fibrous tissue and smooth muscle was noted in the media. Up to a threefold dilatation of vessel caliber occurred in the jugular vein grafts. Johnson and associates noted considerable thickening of the subendothelial portion of saphenous veins used as aortocoronary vein grafts in three patients and this thickening has been observed to be extensive enough to result in severe luminal narrowing or total obstruction of the bypass graft. Grondin and colleagues, in addition to the intimal fibrosis, described fibrotic changes involving the entire vein wall in a patient who died 114 days after bypass grafting.

Vlodaver and Edwards noted changes in each of eight saphenous vein grafts used as aortocoronary bypass conduits in place for more than 100 days: fibrous subendothelial thickening with severe luminal narrowing occurred in six and thrombosis occurred in two. No changes were observed by these authors in venous grafts in place for less than one month.

Marti and associates examined eight grafts at necropsy which were in place up to 300 days and noted wall thickening with intimal hyperplasia and transient medial muscular hypertrophy followed by atrophy and loss of some medial myocytes. Kern and co-workers examined 16 grafts from age 2 days to 29 months both with light and electron microscopy. Intimal fibrosis was present in the nine patients in whom the grafts had been in place for over two months. Ultrastructural study of the intimal lesions showed proliferation of fibroblasts and smooth muscle cells and developing capillaries. Unni and associates studied 62 grafts from 40 patients at various times up to 28 months after operation. The earliest changes were infusion of blood elements into the intima and migration of leukocytes into the media and intima, presumably in response to endothelial damage. The major change after one month was intimal fibrous proliferation resulting in graft occlusion in three patients.

Lipid deposition and atherosclerotic change has been a rare finding in vein grafts in the peripheral circulation and has been reported infrequently in aortocoronary vein grafts. In addition, aneurysmal dilatation which has been observed in canine jugular veins used as aortocoronary grafts is exceedingly rare when saphenous veins are used as aortocoronary conduits. Aneurysm formation in a saphenous vein aortocoronary bypass graft has been reported in only one patient.

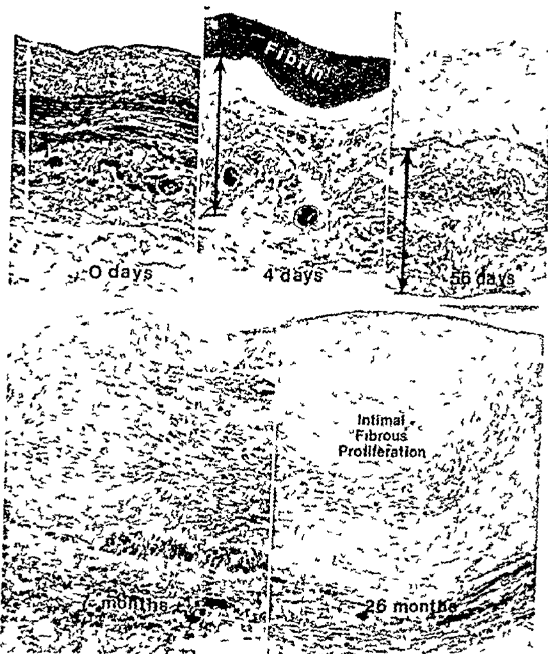


Fig 2 Composite of changes seen in saphenous vein aortocoronary grafts from 0 days (normal vein) to 26 months after implantation *at the same magnification* (×54) Arrows indicate normal wall thickness (media + adventitia) *0 days* = intima thin marked medial smooth muscle layers in both circular and longitudinal directions loose adventitial tissue *4 days* = Large deposit of fibrin over slightly thickened intima Marked loss of medial smooth muscle with cellular infiltration *56 days* = Thickened vein wall with marked intimal fibrous proliferation The media and adventitia show loss of muscle cells and fibrosis *7 months* = Severe intimal fibrous proliferation is present containing some neovascular channels Marked loss of medial smooth muscle and replacement fibrosis is present *26 months* = The vein wall has become almost completely replaced by fibrous tissue and intimal proliferation creating a fibrous tube Only small areas of medial smooth muscle cells remain (All Movat stains)

Brody and associates[17] performed experimental studies of the progression of graft changes in dogs During the first week after implantation they noted endothelial cell damage, fibrin deposition subendothelial edema, and necrosis and inflammatory cell infiltration of medial smooth muscle In later grafts, the medial smooth muscle either hypertrophied died or underwent fibroblastic transformation with resulting medial and intimal fibrosis

Further delineation of the time course of changes in aortocoronary grafts came from Jones and associates[18] in dogs During the first two weeks after implantation the grafts showed focal endothelial disruption, mural fibrin deposition medial edema, and inflammatory infiltration into

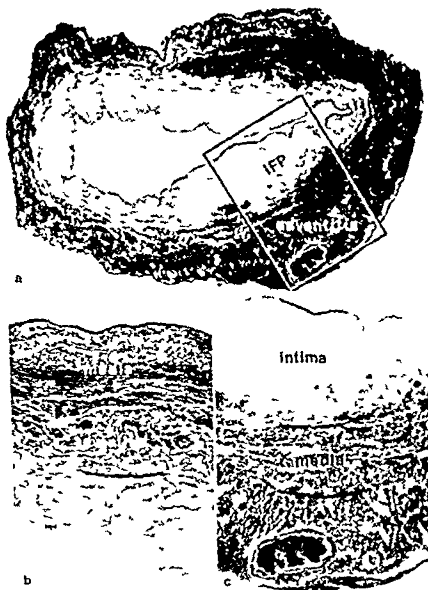


Fig 3 Phlebosclerosis in a saphenous vein used for aortocoronary bypass *grafting (N A75-171) a* Section of a saphenous vein segment left over after use of the major segment for bypass grafting Phlebosclerosis is present creating intimal thickening histologically identical to intimal fibrous proliferation (IFP) *b* Normal saphenous vein for comparison *c* Higher power view of area enclosed in box in *a showing intimal thickening*, loss of some medial smooth muscle and adventitial hemorrhage (Movat stains original magnification ×28 *(a)* ×54 *(b)* ×54 *(c)*)

the vein wall) These changes were followed by loss of smooth muscle cells and the appearance of focal subendothelial proliferative lesions and fibrin deposits By three months diffuse subendothelial fibrous deposits had developed and these became extensive by six to 12 months after grafting

The endothelial changes in grafted autogenous veins have been debated largely because normal histologic and other morphologic studies involve techniques that may produce artifactual losses of endothelial layers Ramos and associates recently described the course and extent of endothelial damage in experimental studies in dogs Progressive changes were seen in all layers of the vein walls including intimal fibrous proliferation

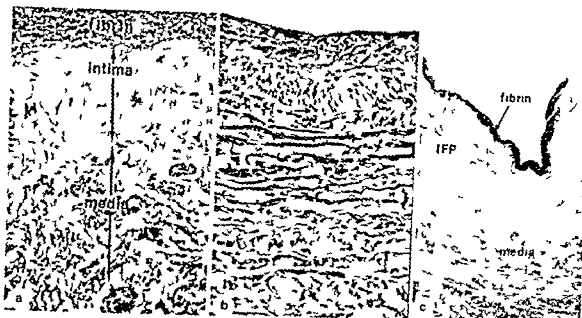


Fig 4 *a* Wall of a vein graft taken 4 days after implantation Fibrin deposition on the intimal surface and infiltration of the intima and media with acute inflammatory cells is seen Necrosis of medial smooth muscle also is present *b* Vein graft implanted for 18 days showing edema and necrosis of medial smooth muscle cells (Hematoxylin and eosin stains original magnification ×220 [*a* and *b*]) *c* Subendothelial fibrin in a 2 month old vein bypass graft Marked intimal fibrous proliferation *(IFP)* is present and loss of smooth muscle in the media is noted (Phosphotungstic acid-hematoxylin stain original magnification ×54)

Endothelial cell layers were sloughed but re endothelialization occurred in all grafts In veins distended with saline before implantation the changes occurred earlier (two to four weeks) and were more severe than in nondistended veins Distention with blood tended to cause less endo thelial damage but ultimately no difference in the degree of fibrotic changes in the vein walls

Personally studied saphenous veins used as aortocoronary bypass conduits in humans

We have examined at necropsy 65 saphenous vein grafts from 38 patients who died up to 72 months after aortocoronary bypass procedures A composite of the histologic changes in these grafts from day zero (normal unused vein) to 26 months after operation is shown in Fig 2 Vein grafts from patients who died intraoperatively showed mini mal medial edema and disruption of the adven titia due to dissection and excision of the vein before grafting In several patients (Fig 3) marked intimal thickening was present in grafts which had been in place for only a few hours Preexisting phlebosclerosis is considered the etiology of the intimal changes in these grafts

By two weeks mural edema was more pronounced, some medial smooth muscle cells were necrotic and inflammatory infiltrates were present The edema was evidenced by the presence of clear spaces between the layers of smooth muscle (Fig 4) The endothelium often appeared disrupted and the intimal surface usually was covered either partially or complete ly, by fibrin

By three weeks cells with characteristics of smooth muscle appeared in the subendothelial portion of the intima The cells generally were oriented such that their longest diameter was parallel to the direction of blood flow (Fig 2)

In grafts in place from two to 72 months the subendothelial intimal lesions were more general ized and less cellular, ground substance was present in abundance and short elastic fibers and vascular channels occasionally were present Deposits of fibrin also often were present both on the luminal surface and in the subendothelial lesions themselves (Fig 4) The smooth muscle fibers of the media now were markedly dimin ished in numbers and they were replaced in part or in whole by fibrous tissue and collagen In the adventitia there was a marked increase in fibrous tissue with severe disruption or complete replace ment of elastic fibers Organizing fibrin on the external surface of the grafts contributed to the adventitial fibrosis (Fig 5*c*) Vasa vasorum were infrequent but capillary channels were present and extended into the fibrotic media in several patients Thus the saphenous vein used as an artery became a stiff fibrous-tissue conduit

The subendothelial proliferation of fibrous

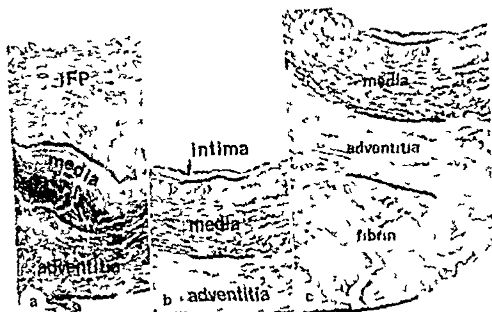


Fig 5 Variable intimal fibrous proliferation *(IFP)* in a 56-day-old saphenous vein graft from a 4 year-old man (A 1 94) who died of renal failure after aortic and mitral valve replacements and vein grafting to the right and left anterior descending coronary arteries. *a* Proximal vessel There is marked IFP and smooth muscle loss in the media. *b* Distal vessel. Minimal IFP is present *c* Adventitial fibrosis and organizing fibrin in same area of graft as *b* (Movat stains original magnification of each ×54)

tissue was quite variable in magnitude and location and infrequently was extensive enough to cause severe narrowing Occasionally it was seen to involve the base of venous valves (Fig 6) Two grafts (7 months and 56 months) did show complete occlusion from intimal fibrous proliferation yet the occlusions were only within 2 cm of the proximal (aortic) anastomosis and the intima of the distal portion of the grafts appeared minimally changed A later graft (26 months) showed changes similar to a 2 month old graft in which luminal narrowing of about 50 per cent was seen In one 19 month old graft very little intimal thickening was present but large collections of subendothelial cells resembling smooth muscle cells were seen (Fig 7) In addition this graft showed extensive subendothelial fibrin deposition Thus the intimal fibrous proliferation appeared to progress at varying rates and locations and often stabilized at some ill defined degree of luminal narrowing

Causes of morphologic changes in saphenous veins used as aortocoronary conduits

Although the causes of the above described changes in saphenous vein grafts are unclear several possible mechanisms have been proposed [1, 11, 12] (Table I) Similar subendothelial proliferation of smooth muscle cells is seen in several situations in the vascular system The phlebosclerotic lesions in venous varicosities are presumably the response of the vein to increases in hydrostatic pressure [3] Arteriovenous shunts of any origin (congenital traumatic or iatrogenic) show intimal thickening presumably the result of

Table I Causes and consequences of changes in veins used for arterial conduits

Cause	*Consequence*
1 Endothelial damage a Trauma b. Elevated transmural pressure 2. Thrombosis 3. Intimal damage 4 Increased wall O tension	Intimal fibrous proliferation
5 Medial ischemia a Loss of vasa vasorum b Increased transmural pressure	Medial fibrous replacement
6. Adventitial ischemia	Adventitial fibrous proliferation

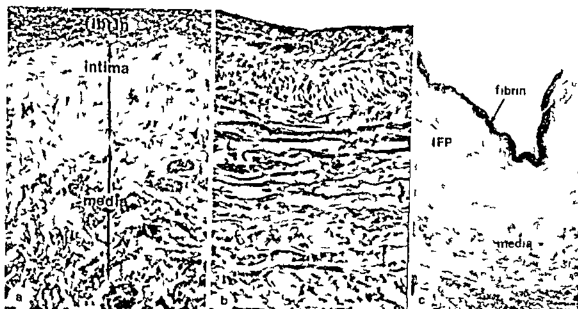


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The subendothelial proliferation of fibrous



Fig 7 Subendothelial myointimal cell accumulation in a 19 month-old graft to the circumflex coronary artery from a year-old man (GT A-69) who died at reoperation for replacement of an occluded graft to the left anterior descending coronary artery *a* Marked medial and subendothelial cellularity is noted. *b* Higher power view showing subendothelial collections of cells, intimal thickening and increased cellularity of the media *c* Myointimal cells are seen immediately under the endothelial layer Beneath these cells is proliferative intimal tissue (Movat stains original magnification ×54 *(a)* ×130 *(b)* ×270 *(c)*)

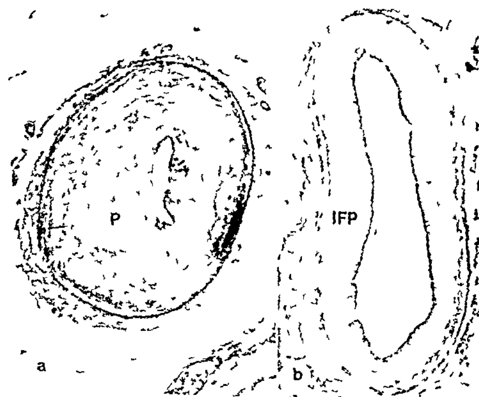


Fig 8 Similarity of atherosclerotic plaque *(P)* in a coronary artery *(a)* and the intimal fibrous proliferation *(IFP)* in a 26-month-old saphenous vein coronary bypass graft *(b)* Both show intimal thickening by fibrous tissue and loss of medial smooth muscle layers (Movat stains original magnification ×16 *(a)* and ×15 *(b)*)

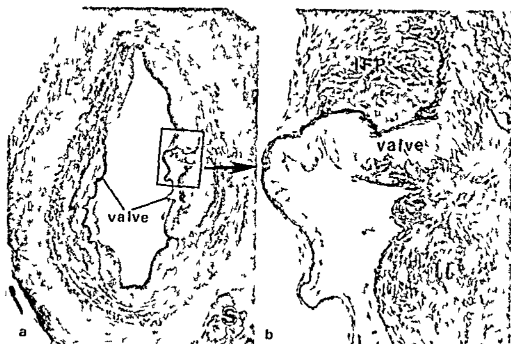


Fig 6 Development of intimal fibrous proliferation *(IFP)* behind venous valves in a 56 day old saphenous vein graft (A71 94) *a* Intimal fibrous proliferation lines the vein graft The valve leaflets are not bound down against the vein wall Marked adventitial fibrosis also is present *S* = suture *b* Enlargement of area shown in box in *a* showing *IFP* above and behind the venous valve The leaflet remains relatively uninvolved (Movat stains original magnification ×23 *(a)* and ×130 *(b)*)

Table II Effects of pressure and ischemia on venous conduits*

Vasa vasorum intact	
Low pressure (venous)	High pressure (arterial)
↓	↓
Normal histology	Intimal proliferation and fibrosis
Intact myocytes	Intact myocytes
Vasa vasorum interrupted	
Low pressure (venous)	High pressure (arterial)
↓	↓
Medial fibrosis	Intimal proliferation and fibrosis
Loss of myocytes	Medial fibrosis Loss of myocytes

Modified from Brody *et al* J Thor Cardiovasc Surg **64** 847 197?

increased pressure and flow [1, 3] Subendothelial proliferative lesions also occur in the small pulmonary arteries of patients with pulmonary hypertension [3, 37] in vena cava and portal veins in patients with chronic right sided congestive cardiac failure or portal hypertension [38, 39] and in peripheral arteries of some patients with systemic hypertension [41] In addition the subendothelial intimal lesions resemble the fibrous and musculoelastic plaques of atherosclerosis[41, 46] (Fig 8)

The common denominator in each of the above examples appears to be an elevation of intravascular pressure or magnitude of flow or both or a decreased velocity of flow with resulting increased shear stress on the vascular walls [6, 15, 4, 18] Brody and colleagues[17] attempted to differentiate the effects of pressure and ischemia on femoral vein grafts in dogs Vein segments were either left intact or dissected free from their adventitia thereby severing the vasa vasora and producing medial ischemia Next the vein segments were either left in the venous system or were arterialized by creation of an arteriovenous fistula The presence of medial ischemia in the absence of elevated pressure and flow produced medial fibrosis in the vein without subendothelial intimal proliferative lesions (Table II) Elevated intravascular pressure alone however without alterations in blood supply to the media by the vasa vasorum produced intimal lesions without evidence of medial fibrosis The combination of both elevated intraluminal pressure and medial ischemia resulted in medial and intimal changes similar to the changes seen in human saphenous veins used as aortocoronary conduits

Several factors unique to aortocoronary bypass grafting make the changes of ischemia and pressure more likely in these grafts than in grafts used



Fig 7 Subendothelial myointimal cell accumulation in a 19 month-old graft to the circumflex coronary artery from a 5 year-old man (CT 5A-C0) who died at reoperation for replacement of an occluded graft to the left anterior descending coronary artery *a* Marked medial and subendothelial cellularity is noted *b* Higher power view showing subendothelial collections of cells, intimal thickening and increased cellularity of the media *c* Myointimal cells are seen immediately under the endothelial layer Beneath these cells is proliferative intimal tissue (Movat stains original magnification ×54 *(a)* ×130 *(b)* ×220 *(c)*)

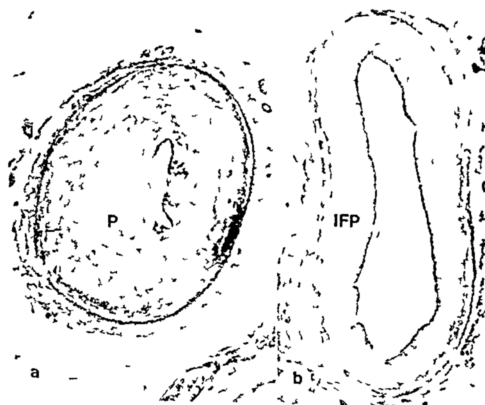


Fig 8 Similarity of atherosclerotic plaque (*P*) in a coronary artery *(a)* and the intimal fibrous proliferation *(IFP)* in a 96-month-old saphenous vein coronary bypass graft *(b)* Both show intimal thickening by fibrous tissue and loss of medial smooth muscle layers (Movat stains original magnification ×16 *(a)* and ×15 *(b)*)

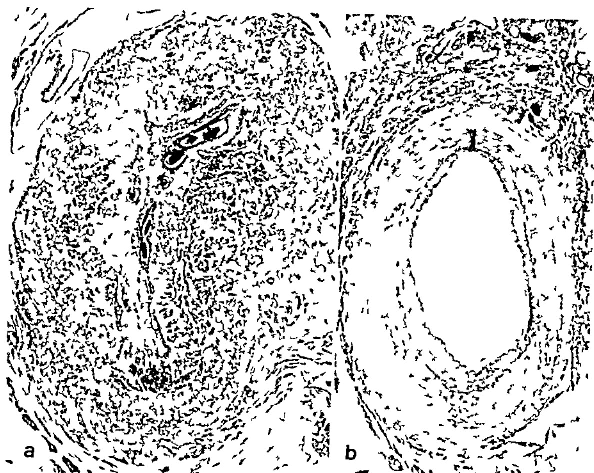


Fig 9 Saphenous vein bypass grafts from a 44 year old woman (7983) who underwent grafting to the right *(a)* and left anterior descending (LAD) *(b)* coronary arteries 26 months before death She died suddenly at home *a* Right coronary graft showing occlusion and recanalization of the lumen with little intimal fibrous proliferation (IFP) Thrombus was the probable cause of graft occlusion *b* LAD graft showing moderate IFP and marked adventitial fibrosis (Movat stains original magnification of each ×27)

Table III Venous conduits for aortocoronary bypass Factors promoting fibrinous or fibrous intimal proliferation with or without occlusion

1 Severe narrowing distal to insertion of the graft
2 Insertion of graft in area of plaque
  a Thrombosis
  b Hemorrhage
  c Dissection
3 Hyperacute angle of aortic anastomosis (90 optimal)
4 Tension on grafted vein
  a Decreases flow
  b Damages endothelium or intima
  c Causes tension on anastomoses
5 Previous sclerosis of vein used for conduit
6 Overdistension of vein with saline
  a Damages endothelium and intima
  b Possible direct effect on phospholipids of smooth muscle

in the peripheral circulation While the excised vein is revascularized early when placed in the highly vascular tissue beds in the extremities[4] the unsupported nature of the grafts in the aortocoronary position make delay in revascularization of the media more likely Furthermore flow occurs under diastolic not systolic pressure in the coronary system and flow consequently is slower[11, 4]

The mechanisms whereby pressure and ischemia cause the intimal and medial changes are unclear (Table III) Brody and associates[16] suggest that both the intimal and medial changes are produced by the transformation of medial myocytes in response to injury or to change in their nutritional status The myocyte response may be mediated by elevated wall oxygen tension with resulting effects on phospholipid[18, 50] or by the presence of plasma factors or blood products as a result of recurrent endothelial damage[7, 15, 16] The medial myocyte may be transformed into a fibrocyte[1, 1] resulting in medial fibrosis or it may become a myointimal cell and migrate to the intimal layer in response to some unknown stimulus to produce intimal thickening[17, 51]

That the degree of fibrous intimal proliferation is often variable along the length of a vein graft[11, 1] (Fig 5) or between two grafts in the

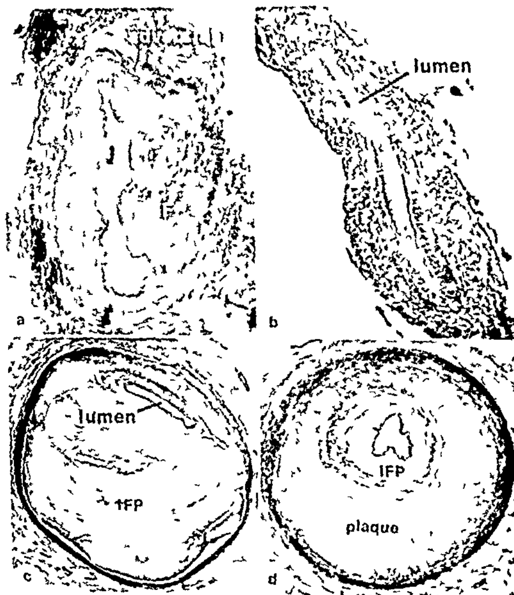


Fig 10 Saphenous vein graft from a 31 year-old man (A) 79) who died 7 months after placement of a graft to the left anterior descending (LAD) coronary artery Endarterectomy was done at the site of the anastomosis to the coronary He did well for 6 5 months when angina returned At reoperation the vein graft *(a)* was found to be narrowed proximally by intimal fibrous proliferation *(IFP)* and flattened and sclerosed distally *(b)* He died after repeat bypassing of the LAD and placement of vein *grafts to the right and posterior descending* coronary arteries. c Section of LAD immediately distal to the anastomosis of the vein graft at the area of previous endarterectomy showing almost complete occlusion of the vessel by fibrous tissue plaque *(IFP)* *Only a tiny lumen remains* Th IFP extended down the LAD for several centimeters and appeared to be superimposed on preexisting plaque *(l)* further narrowing the lumen of the vessel (fcvat stains original magnification ×?0 *(a)* ×22 *(b)* ×31 *(c)* ×45 *(d)*)

same patient (Fig 9) indicates that elevated pressure alone does not account for the extent of changes in these conduits Some anatomic and technical factors therefore must modify the effects of pressure and ischemia on the grafted vein and the distal coronary artery These factors which are listed in Table III are all related in some fashion to the amount of flow or to the *velocity or turbulence* of flow in the graft or the coronary artery into which the graft inserts

Faulkner and associates studied the effect of flow rate on the development of subendothelial proliferative lesions in femoral vein grafts in dogs Grafts subjected to low flows (30 to 50 ml /min)

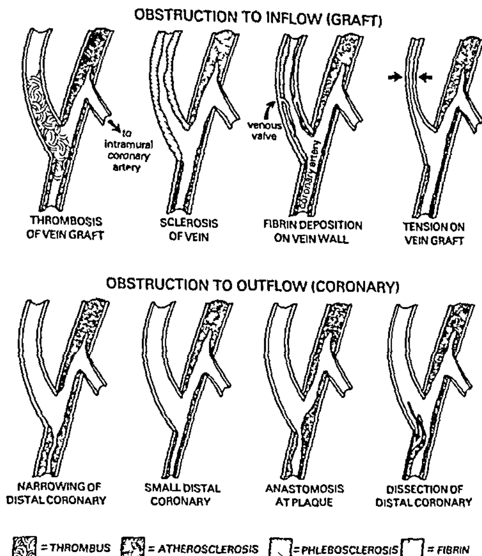


Fig 11 Anatomic and technical factors that affect flow in the coronary arteries following aortocoronary bypass

showed significantly greater and more generalized intimal proliferation than grafts subjected to high flows (790 ml/min average) Subendothelial intimal proliferation, however occurred in all grafts just distal to the proximal anastomosis and at the distal anastomosis in both the vein and the native artery, indicating that turbulence of flow caused by the anastomosis produces augmented vein response, perhaps by causing localized recurrent endothelial disruption [6 9 18] Elevations in pressure, therefore, may result in recurrent endothelial damage which is then converted to intimal lesions by progressive fibrin deposition High flow states may keep the endothelium washed of thrombi while low flow may encourage such thrombi and result in significant luminal narrowing

Jones and associates[18] offer support for the concept that progressive intimal fibrous proliferation may be the result of progressive organization of subendothelial or mural deposits of fibrin which accumulate as a result of recurrent endothelial damage It is well known that fibrin and platelet thrombi accumulate in response to exposure of collagen basement membrane or elastin to the blood [ ] and that mural thrombi may become incorporated into plaques [ ] In addition fibrous lesions similar to those seen in bypass grafts occur in native coronary arteries after endothelial damage from perfusion cannulae or after endarterectomy (Fig 10) [ ] Fibrin deposition on venous valves has been implicated in causing stenoses of femoropopliteal vein grafts [ ] The laminated appearance of some areas of subendothelial intimal proliferative lesions in vein bypass grafts and the new vascular channels in the plaques themselves plus the histologically demonstrable fibrin deposits in some subendothelial lesions (Fig 4) lend support to the concept of continued organization of thrombi as the etiology

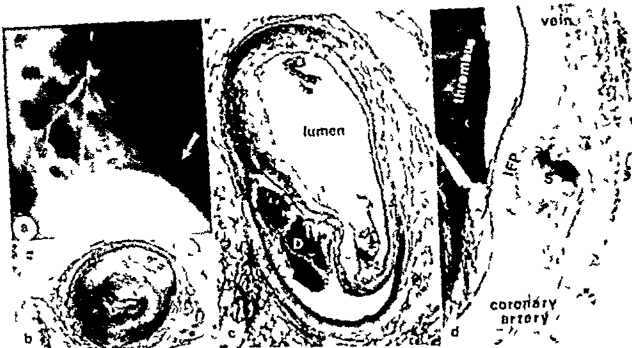


Fig 12 *a* and *b* Severe obstruction of coronary artery distal to the site of insertion of a vein bypass graft in a 40-year-old woman (A 4 21?) who could not be weaned from cardiopulmonary bypass after 3 vessel vein grafting *a* Preoperative coronary angiogram showing total occlusion of the left anterior descending (LAD) coronary with reconstitution distally The distal vessel was interpreted as showing no significant narrowing *b* Section of LAD vessel at approximate area shown by *arrow* in *a* Severe narrowing of the vessel is seen despite a normal appearing angiogram. *c* Coronary artery dissection in the left circumflex coronary artery after bypass grafting (A72 709) The dissection *(D)* has progressed distally narrowing the lumen of the vessel. *d* Intimal fibrous proliferation *(IFP)* extending into the coronary artery at the site of vein graft anastomosis in a patient (PHWT A73-28) who died suddenly at home 34 days after bypass grafting to the right coronary artery Section taken at the venocoronary anastomosis showing antemortem thrombosis of the vein graft extending into the coronary artery (CA) and moderate intimal fibrous proliferation *(IFP)* of the vein with extension across the suture line *(S)* into the coronary artery (Movat stains original magnification ×2? *b* ×38 *c* ×31 *d*)

of these lesions In addition the histologic similarity of recanalized thrombus to intimal fibrous proliferation has been described in grafts in dogs[34]

The anatomic and technical factors which may alter blood flow in saphenous grafts may be divided into two groups (1) those that limit inflow (refers to the status of the graft itself) and (2) those that limit outflow (refers to the status of the coronary artery into which the graft inserts) (Fig 11) Any of these factors may result in fibrous subendothelial intimal proliferation or thrombosis of the graft or both

Studies of the coronary bypass grafts (37 saphenous veins) and native coronary arteries in 20 patients who died early (< 2 months) after aortocoronary procedures were carried out to evaluate the frequency of the presence of any anatomic or technical factors that might lead to decreased graft flow[3] Two of the 37 grafts were occluded by thrombus but the remaining 35 were free of occluding thrombus Fibrin deposits (usually small) were present on the walls of 27 per cent of the grafts (Fig 2) and 29 per cent of the coronary arteries at or near the site of the anastomosis Fibrin also was present proximal to the anastomosis in some patients and occasionally the proximal artery was thrombosed probably due to the watershed effect of a subtotal proximal obstruction[3]

In 38 graft systems (graft plus the entire coronary artery into which the graft inserted) sections of the anastomosis were adequate to estimate degrees of luminal narrowing In one graft the lumen of the coronary artery was > 75 per cent narrowed at the anastomosis itself while in seven it was 51 to 75 per cent narrowed by atherosclerotic plaque at this point Significant

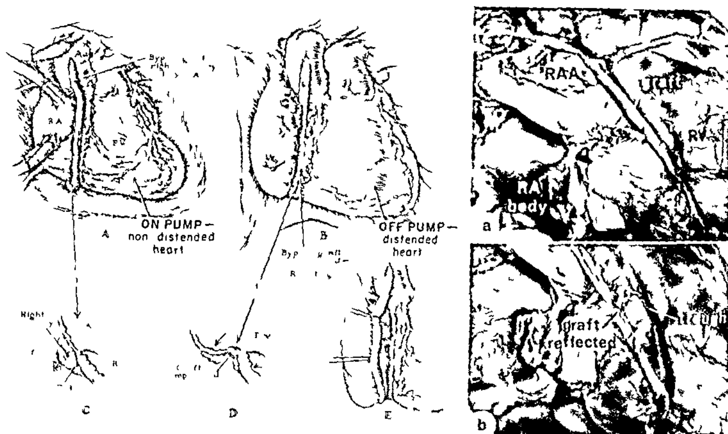


Fig 13 Tension produced on a vein graft to the right coronary artery *Left A* and *C* Patient on bypass heart empty The vein graft passes along the atrioventricular (AV) sulcus without tension *B* and *D* Patient off bypass heart beating Distension of the right atrium and ventricle compresses the vein graft in the AV sulcus *E* Reflection of the vein graft shows the trough which results from excessive tension *RA* = right atrium *R V* = right ventricle *Right* Saphenous vein aortocoronary bypass graft from the aorta *(dashed circle)* to the right posterior descending coronary artery (RCA) in a 49 year old man (GT 75A 107) who died 2 hours after operation from refractory hypotension *a* The graft passes along the right atrioventricular (A V) sulcus below the ligated right atrial appendage *(RAA)* and the right atrial body *b* A view of the graft after it has been reflected A deep trough is present in the A V sulcus indicating that the graft was under significant tension *RV* = right ventricle

obstruction to graft flow might be expected in these patients In some grafts intimal proliferation extended from the vein graft across the anastomosis and into the distal artery (Fig 12*d*)

Dissection of the coronary artery at or near the anastomosis due primarily to separation of atherosclerotic plaque occurred in seven (19 per cent) graft systems studied (Fig 12*b*)

Atherosclerotic narrowing of the coronary artery distal to the anastomosis of the aortocoronary bypass graft often was pronounced Significant (> 75 per cent) cross sectional narrowing in this segment occurred in 16 (44 per cent) of the graft systems examined (Fig 12*a* *b*) Narrowing of 51 per cent to 75 per cent occurred in an additional 31 per cent Thus residual severe atherosclerosis in the native coronary artery distal to the graft anastomosis is the most frequent cause of poor graft run off

Small caliber of the coronary artery distal to the vein graft anastomosis also has been suggested as a factor which may decrease flow through the graft While estimates of what constitutes a small distal artery are debated measurements of *relative* vessel size in men versus women after bypass grafting indicates that vessel size in women is smaller than in men even when rough correction is made for variations in cardiac weight [59-61] Luminal areas however are similar when correction is made for myocardial mass, suggesting that less atherosclerotic narrowing is necessary to produce a given limitation to blood flow in women than in men While coronary size *per se* may not be important in terms of over all blood flow the smaller coronary arteries in

women may make creation of the venocoronary anastomosis more difficult technically. This feature may contribute to the higher (2 times) early mortality rate in women than in men after saphenous vein aortocoronary bypass operation.[illegible]

A possible but neglected cause of obstruction to graft flow is tension on the graft caused by underestimation of graft length at operation or by excessive cardiac distention postoperatively[4] (Fig. 13). In a study of 41 saphenous vein aortocoronary grafts from 21 patients at necropsy, abnormal graft tension (as indicated by grooving of the right atrial wall or right atrioventricular sulcus [Fig. 13] or by flattening of a graft passing in front of the pulmonary trunk) was present in six grafts (15 per cent) from five patients (24 per cent). The abnormal graft tension was observed in five (33 per cent) of 15 grafts to the distal right or posterior descending coronary artery but in only one (3 per cent) of 26 grafts to left coronary arteries. Graft tension appeared to result from placement of a graft of inadequate length to accommodate normal or abnormal distention of the right atrium and right ventricle or of the pulmonary trunk after discontinuation of cardiopulmonary bypass or development of congestive cardiac failure. Localized graft occlusion also may occur as a result of local hematoma formation and tamponade.

The hydraulics of the angle of take off of the graft from the aorta may influence graft flow and therefore may predispose to graft occlusion by thrombosis or intimal fibrous proliferation. The optimal angle for maximal flow and minimal turbulence has been calculated to be 90 degrees. Among eight patients studied by Kennedy and associates, the angle of the aortic anastomosis ranged from 30 to 80 degrees (average 45 degrees). Even when the graft initially is placed at an angle of 90 degrees to the aorta, shortening later may cause this angle to become more acute. Although experimental studies of vein grafts in the peripheral circulation indicate that greater intimal fibrous proliferation occurs in grafts placed at an acute angle,[66] examination of aortocoronary bypass grafts in 13 dogs with either acute, obtuse, or perpendicular take off of the aortic anastomosis showed no effect of the angle of the aortic anastomosis on the location or severity of the intimal changes.

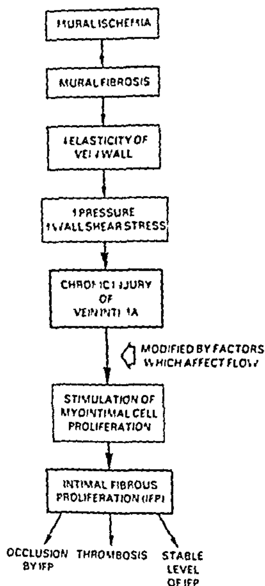


Fig. 14. Summary of the relationship of various factors to the development of graft changes and the ultimate fate of the graft.

The frequency of aortocoronary saphenous vein bypass graft occlusion from thrombus or fibrous intimal proliferation appears to be decreasing. The reasons for this decrease are not known, but less traumatic handling of the vein before implantation and changes in the population of patients considered for bypass procedures may be large contributing factors. Although probably all vein grafts develop some intimal thickening with time, relatively few become totally occluded by this proliferative process. It is likely that this variation in the ultimate fate of

grafts is related to the relative contributions of the various factors affecting graft flow These are described above and outlined in Fig 14 Perhaps stabilization of the degree of intimal proliferation occurs when flow has been modified to become less turbulent and damaging to the endothelial layer or when the caliber of the graft approaches that of the distal coronary artery into which it inserts If severe alterations in flow occur at this stage progression to complete occlusion by thrombosis may result Early graft thrombosis would be expected in situations where restrictions to flow were severe soon after operation

Although the explanation for the development of occlusion or stenosis of saphenous vein aorto coronary grafts remains speculative we believe that progressive injury to the vein by elevated pressure and modified by several anatomic and technical factors which affect flow results in progressive exposure of collagen to plasma factors or fibrin deposition with resulting stimulation of smooth muscle cells Further study of the relative contributions of the various influencing factors may permit alterations in surgical technique or patient selection to minimize both early and late graft failures

Summary

This report describes morphologic changes in saphenous veins used as aortocoronary bypass conduits and discusses the relative contribution of various factors to these changes The three primary changes are (1) *medial fibrous replace ment* (2) *adventitial fibrous proliferation* and (3) *intimal fibrous proliferation* Medial fibrous replacement is caused by vein wall ischemia with loss of smooth muscle cells, adventitial fibrous proliferation is the result of organization of fibrin deposits and repair of ischemic injury, and intimal fibrous proliferation results from some stimulus probably fibrin deposition on injured intima, which causes stimulation of smooth muscle cells to become fibroblasts or myointimal cells Although all grafts show some changes the degree and severity of these three changes is variable along the length of the grafts and among separate grafts in the same patient

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Cardiac pacing and pacemakers VII Power sources for implantable pacemakers Part I

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Because premature battery exhaustion was very common in the last decade the major thrust of research was directed toward the development of better batteries The nuclear battery attended by considerable publicity and some controversy was the first of the new systems to be launched [1-4] Later but less dramatically the lithium cell under study since 1967 reached the market it has now all but taken over the industry [5]

The several types of battery now in use are 1 Primary cells—mercury/zinc 2 Secondary cells—rechargeable—chiefly nickel/cadmium and possibly modified mercury/zinc 3 Lithium cells—solid state and organic 4 Radioisotope cells (nuclear)—really a power generator rather than a battery

A brief review of how a standard chemical battery works will be of some help in understanding how the new models differ The basic *unit* is the electro chemical cell (Fig 1) One of these if used alone or several if used together constitute a battery Normally a cell consists of a single positive electrode or cathode a single negative electrode or anode and an ionically conductive element or electrolyte in contact with both electrodes When an electrical conductor or circuit is connected from anode to cathode the electrons flow through the external circuit to the cathode providing power for the pacemaker circuit

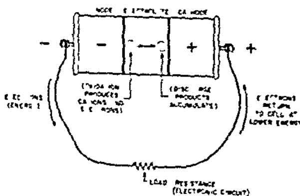
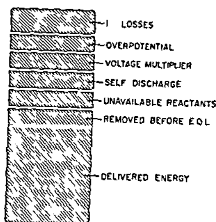


Fig 1 Simplified drawing of a basic chemical cell.

A chemical reaction occurs at both electrodes and the cathode and anode materials are depleted or altered The amount of active material present at the beginning of life (BOL) determines how many electrons the battery can pass through the circuit before this material is used up and limits the battery usefulness at the end of life (EOL) The total quantity of charge is called the *coulombic capacity* of the cell It is commonly measured in ampere hours The product of coulombic capacity and average open circuit voltage is the amount of energy the cell theoretically can deliver The ratio of theoretical cell energy to battery weight (mass) is known as gravimetric energy density The ratio of theoretical cell energy to battery volume is volumetric energy density (See Table I for relative energy densities of common cells) In practice *usable* capacity falls well below *theoretical* capacity because cell voltage drops below its open-circuit



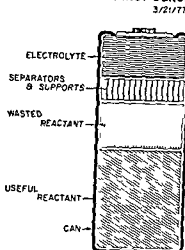


Fig 2 Diagrammatic representation of a battery (*right*) and the major causes of inefficiency due to internal and external losses (*left*)

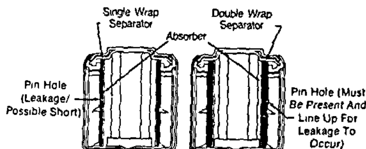


Fig 3 Schematic diagram of a mercury/zinc cell The early Mallory RM 1 cell is on the left and the improved double wrap RM 2 cell on the right

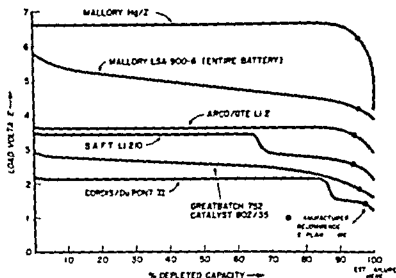
value when current is drawn especially if the internal impedance of the cell becomes comparable with that of the external circuit and because the full amount of reactive material present at BOL cannot be 100 per cent consumed Useful cell energy is also reduced if the chemical reactants are consumed without at the same time propelling electrons through the pacemaker circuit Such losses are called *self discharge*

Self discharge occurs in several ways When an additional electrically conductive path is present from anode to cathode the cell reaction proceeds normally but some electrons follow the internal path and do no useful work Such a path develops if some material between the electrodes becomes electronically conductive during discharge because of dendritic growth of active or inert electrode material This process accounted for many early mercury/zinc cell failures when free dendritic growths of metal shorted out the cell The 'double wrap" separation of cathode and electrolyte, and the addition of silver to the cell to form a mercury—silver amalgam helped eliminate this cause of premature cell failure There is also self discharge when a chemical reaction occurs without an electrically conductive path from anode to cathode in which case the anode or cathode may be consumed without doing useful work Self discharge also occurs when active material from one electrode reaches the opposite electrode before being ionized or reduced generally by a process of diffusion

All these self discharge processes depend in complex ways on the geometry and chemistry of the cell and may change as the cell discharges For this reason it is difficult to predict lifetime self discharge losses for a battery on the basis of short term accelerated tests The various losses as well as other factors such as overpotential and the use of a voltage multiplier may prevent a substantial amount of the reactants from doing any useful work The reactants which remain are converted into useful energy which determines how much pacing life a cell can provide Fig 2 shows schematically why the useful energy density of a battery may be only a small fraction of its theoretical energy density

Mercury/zinc cells

The Mallory RM 1 mercury/zinc cell once the workhorse of the industry is still an acceptable power source (Fig 3) (A similar Swiss type, the LeClanche cell was formerly found in many European units) As seen in Fig 4 its voltage tends to remain constant throughout its life Its popularity has waned somewhat because of its irregular failure modes the significant internal losses the generation of gas that must be



ESTIMATED DISCHARGE PROFILE AT PACEMAKER DRAIN RATES

Fig. 4. Voltage course of various lithium cells as compared to a mercury/zinc cell (Hg/Zn).

absorbed by a "getter" or vented to the outside and the theoretical dangers of incineration.

Multi celled batteries may have several advantages over single celled batteries. When two or more cells exist they may be interconnected in series or in parallel, or in a combination series parallel configuration. The last arrangement, sometimes called a redundant connection, can provide a backup power system should one of the cells fail. Not all multi cell connections are redundant, however. Two-cell batteries are often designed to operate on one cell at a time, and when a shift to the second cell occurs it will be reflected in a change of pacemaker rate. Even more complex safeguard arrangements are found in four cell systems.

Certain objectives must be considered in the search for an ideal battery. The battery should have high gravimetric and volumetric energy density to provide maximum pulse generator life and to reduce pacemaker size and weight. It should have sufficient open circuit voltage to obviate the need for voltage doubling circuits that are wasteful of energy. Hermetic sealing may be important to prevent water leaks into the cell and corrosion product or gas leaks out of the cell. The cell configuration should be flexible enough to accommodate the desired shapes of the pulse generator. Self discharge losses should be minimal. The battery should decay slowly and predictably so that the clinician will have sufficient

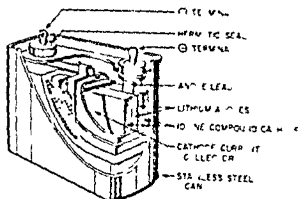


Fig. 5. Diagram of an early lithium iodide cell manufactured by Wilson Greatbatch, Ltd.

leeway to replace the pacemaker electively when signs of impending battery failure are detected.

To meet these aims, there are several types of cells under study, but actually only three of them have reached the market—rechargeable nickel cadmium (NiCad), lithium of various kinds, and nuclear. Other cells, such as bromine and special rechargeable batteries are under intensive investigation.[11, 12]

Rechargeable cells

A pulse generator with a single rechargeable NiCad battery (Pacesetters) has been on the market for several years. The pacemaker has two components: the implantable pulse generator and

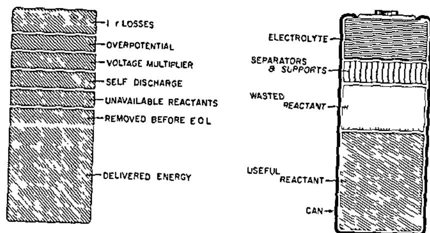


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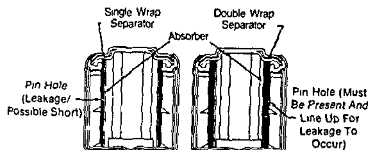


Fig 3 Schematic diagram of a mercury/zinc cell The early Mallory RM 1 cell is on the left and the improved double wrap RM 2 cell on the right

value when current is drawn, especially if the internal impedance of the cell becomes comparable with that of the external circuit and because the full amount of reactive material present at BOL cannot be 100 per cent consumed Useful cell energy is also reduced if the chemical reactants are consumed without at the same time propelling electrons through the pacemaker circuit Such losses are called *self discharge*

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	Other Lithium					
[illegible]	CTF/APCO [illegible] chloride	[illegible]	[illegible]	[illegible]	[illegible]
Li	Li	Li	Li	Li	[illegible]
[illegible] + propylene carbonate	LiAlCl + SOCl	LiI + AlO	[illegible]	LiBr	[illegible]
[illegible]	SOCl C	[illegible]	CuS	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
90	16	40	[illegible]	[illegible]	[illegible]
31	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	410	[illegible]	[illegible]	[illegible]	[illegible]
61	[illegible]	[illegible]	61	[illegible]	[illegible]
None Measured	<1[illegible] in 1 yr	None Measured	None Measured	[illegible] in 10 yrs	[illegible] wk
0.81	[illegible]	0.91	1.8	1	[illegible]
1.9	[illegible]	[illegible]	[illegible]	1	[illegible]
CPI Telect Medcor Edwards LEM	ARCO	Coratomic Intermedics [illegible]	Cordis Double plateau [illegible] [illegible]	[illegible]	[illegible]
No	Yes	Yes	No	Yes	Yes

months or 4[illegible] years as promised by the devel opers of a new rechargeable mercury/zinc cell [illegible]

Lithium systems

There are several reasons why lithium is highly suitable for the pacemaker battery it has a high energy density it forms a strongly reactive cation which yields high cell voltages with a variety of cathode materials in its metallic state it is easily *formed into a variety of shapes and it* is readily available in high purity and at moderate cost There are five lithium systems in widespread use today Two of them utilize another property of lithium they may be made into ionically conductive solid salts with halogens suitable for electrolyte material Lithium iodide is used in both *solid* electrolyte systems The other three lithium systems use liquid electrolytes Features of the five systems and a list of the companies that use them are summarized in Table I

Solid electrolyte systems

Organic iodine cathode No electrolyte is included in cell construction it forms during discharge The cell cathode consists *of molecular* iodine weakly bonded to an organic polymer (polyvinyl pyridine) a crystalline lithium iodide electrolyte *forms between* anode and cathode (Fig 5) When iodide ions are formed at the cathode they become part of the electrolyte crystal This process creates a steady increase of resistance within the cell and an accompanying drop in cell voltage The discharge curve for this system shows a slow fairly linear voltage decrease due to the buildup of electrolyte and a more rapid decrease at end of life due to depletion of iodine in the cathode (Fig 4)

Lead sulfide cathode This system is entirely solid state contains no corrosives and produces no gas even if short circuited The electrolyte is lithium iodide with *aluminum* oxide added to increase conductivity it has no measurable self discharge Lithium iodide is formed during discharge *and here too* conduction becomes more difficult as discharge products accumulate and cell voltage gradually *decreases* with discharge (Fig 6) Seven small cells are stacked in

Table I List of characteristics of pulse generator power cells in clinical use*

	Hg/Zn	Lithium iodide				
		Wilson Greatbatch			*Catalyst research*	
	Mallory RMI	*702E (+CRC)*	*752*	*755*	*802/23*	*802/35*
Anode	Zn	Li	Li	Li	Li	Li
Electrolyte	NaOH +Ag	LiI	LiI	LiI	LiI	LiI
Cathode	HgO	I +P VP	I +P VP	I +P VP	I +P VP	I +P VP
Voltage open circuit/cell	1 35‡	2 8	2 8	2 8	2 8	2 8
Battery weight (grams)	13 8	80	27	33	30	54
Battery volume (cm)	3 0	31	9 5	9 5	11 2	19
Energy density gravimetric W H /kilo	100	110	140	230	200	190
Volumetric W H/cm	45	28	39	79	53	53
Self discharge	Yes 23 μa	<10% in 10 yrs	<10% in 10 yrs	<10% in 10 yrs	<10% in 10 yrs	<10% in 10 yrs
Capacity (B O L A H)	1 0	3 5	1 5	3 0	2 3	4 3
Energy (W H)	1 35	8 75	3 75	7 5	6 0	10 0
Used by (manufacturers)	Most	CPI Telect ELA Devices LFM Siemens	CPI Telect	CPI Telect Cardio France	Amer Tech Intermedics Pacesetter Biomed Vitatron	Amer Pace LEM Med Ital Siemen Sorin Tech Biomed
Hermetic seal	No	Yes	Yes	Yes	Yes	Yes

The list does not include *all* cells that have been designed but does show typical ones from the major manufacturers (In fact Wilson Greatbatch Ltd manufactures more than eight different model cells CRC 4 SAFT 2 and GTF 3 all similar to the example shown above) Only one new lithium cell (Wilson Greatbatch lithium/bromine) has been shown in order to illustrate the potential improvement of continuing industrial research and we have not included a proprietary WG cell the 742 now being marketed by Medtronic The nuclear cells are not shown because in a sense they are not batteries but generators in that the thermal power source is not drained by usage but depends solely upon the natural half life of the plutonium 238 Not included are Hg/Zn rechargeable

Abbreviations Ag = silver Al = aluminum B O L /A H = beginning of life/ampere hours Br = bromine Cl = chlorine H = hydrogen Hg = mercury I = iodine Li = lithium NiCd = nickel cadmium O = oxygen P VP = poly vinylpyridine Pb = lead Pr = praseodymium S = sulpher Zn = zinc Amer Tech = American Technology Inc Amer Pace = American Pacemaker Corp CPI = Cardiac Pacemakers Inc CRC = Catalyst Research Corp Devices = Devices Ltd (England) ELA = Electronique Appliquee (France) GTE = General Telephone & Electric LFM = Flettro Medicali (Italy) Med Ital = Medico Italia (Italy) Siemens = Siemens Elema (Sweden) Sorin Biomed = Sorin Biomedica (Italy) Tech Biomed = Techologie Biomediche (Italy) Telect = Telectronics (Australia) WG = Wilson Greatbatch Ltd

†Voltage of battery (more than 1 cell)

‡Used in batteries of 4 or 5 cells

the external recharger The battery must be recharged one hour a week easily done during leisure hours, but the charge is potentially sufficient to operate the pacemaker at progressively slower rates for approximately eight weeks Present developments indicate that eventually it will be possible to charge the cells at less frequent intervals, and that the pulse generator will continue to operate for many years but it is too early yet to substantiate these claims[13] Care must be taken to place the proper surface of the pacemaker toward the skin or else it will not be possible to recharge the cell There are those who are enthusiastic about the use of the Pacesetters unit and more than 3 100 have been implanted[14] Actually there has been no clear wave of enthusiasm based upon the volume of use of this pacemaker in the United States[15] Some reluctance is due no doubt to a wait and see attitude and some perhaps to a tacit belief that the ideal pacemaker should function without adjustments and maintenance by the patient or his family Possibly these attitudes will change if recharging were required only once every six

or 10 per cent of total battery life) will remain for pacer replacement.

This discharge profile of two battery voltages stems from two reactions that take place in the cell in sequence. The first involves reduction of cupric sulfide to cuprous sulfide and results in higher voltage. When all the cupric sulfide is depleted from the cathode the cuprous sulfide is further reduced to copper by a secondary reaction which results in a lower voltage plateau.

Three of these cells connected in series give a 6.1 volt battery output and obviate the need for a voltage doubler. There is no self-discharge reported in this cell. Cells depleted *beyond* the second voltage plateau may reverse polarity, possibly causing an abrupt drop of pacemaker output and rate. The manufacturer recommends replacement when the rate drops to the value of the second plateau.

Silver chromate cathode. This cell (SAFT) is similar in construction and operation to the cupric sulfide cathode cell. The electrolyte is lithium perchlorate dissolved in propylene carbonate (Fig. 9). Like the CuS cathode cell, this system has a discharge with two voltage plateaus, the first due to reduction of silver chromate to lithium chromate, and the second due to further reduction to a more stable chromium oxide and lithium oxide. Replacement is recommended when the end of the second plateau is reached.

Discharge products occupying considerably more space than reactants accumulate in the porous separators and swell the outer battery case as discharge proceeds. Cell halves are held together by a polypropylene gasket crimped between stainless steel cups. The polypropylene is impermeable to the liquid electrolyte but is gas permeable (non hermetic). Self discharge is reported to be negligible. When two cells are used in parallel, pacers require a voltage doubler.

Clinical experience with lithium pacemakers. Pulse generators powered by lithium batteries were implanted first in early 1972 and are now manufactured by every pacemaker company. The experience at the Newark Beth Israel Medical Center in 1976 (Table II) illustrates the extent of their use and suggests that within a few years lithium powered cells will replace the older mercury/zinc units entirely. Enough of these units have been used at the Newark Beth Israel

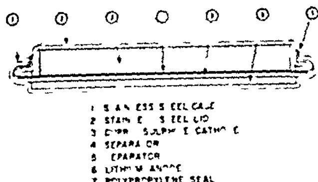


Fig. 8. Diagram of lithium cupric sulfide cell (Cordis/DuPont).



Fig. 9. Diagram of lithium/silver chromate cell (SAFT).

Table II. Types of pacemakers in service—December 31, 1976, 641 units (Newark Beth Israel Medical Center)

Power source	*Per cent of total*	*Projected new pacers for 19––**
Mercury/zinc	47	10%
Regular output	18%	
Reduced output	3%	
Lithium	30%	80%
Nuclear	1%	10%
Rechargeable	<0.1%	0%

*These figures represent the personal preferences (and prejudices) of the Hospital Pacemaker Center.

Medical Center to provide the cumulative survival curves seen in Fig. 10. Similar results have been reported by others.[11,12] There have been more than 20,000 lithium implants in the past five years and so far there have been no *battery* failures. Component failures have been rare, occurring at a rate of less than 0.3 per cent per year.

It is fallacious, however, to discuss lithium cells as if they were all one and the same. As can be seen in Table I, there are many types of lithium cells used in commercially available pacemakers.

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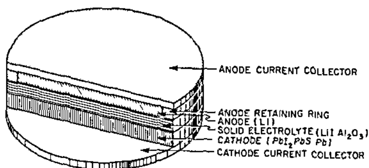


Fig 6 Drawing of basic construction of Mallory lithium/lead sulfide cell

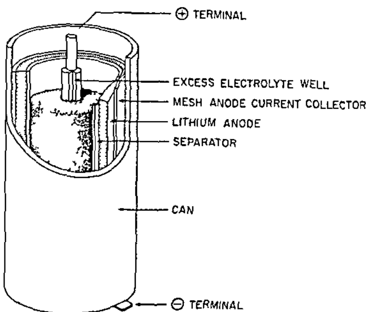


Fig 7 Diagram of GTE thionyl chloride cell

a single can, a spring is used to maintain contact between them The battery in clinical use today consists of three stacks of seven cells in a series-parallel array The battery will continue to function even if three cells fail Failure of a single cell changes battery voltage by less than 0 2 volts

Liquid electrolyte systems

Thionyl chloride cathode A lithium cell with a thionyl chloride cathode (GTE/ARCO) has greater energy density than most competitive systems (Fig 7) The cathode consists of a porous carbon black rod with a hole in the center to accommodate the cathode current collector The electrolyte consists of lithium tetrachloroaluminate dissolved in thionyl chloride * One feature that distinguishes this system from others and accounts for its high energy density is the participation of the electrolyte solvent in the discharge reaction Two discharge reactions have been proposed for this system one of them produces elemental sulfur and the secondary one generates sulfur dioxide gas all of which can be accommodated within the hermetically sealed battery can without pressure buildup Although the self discharge current in this battery is higher than with other lithium systems, the rate of self discharge is said to be less than 1 0 per cent a year The cell maintains its open circuit voltage for almost the entire life of the cell At EOL a gradual voltage decrease is seen which should provide ample warning for pacer replacement In a pacemaker a pulse voltage doubler is required to provide a 6 5 volt pacer output, but the high energy density of the cells more than compensates for the energy loss because of this

Cupric sulfide cathode Another liquid electrolyte system (Cordis/Dupont) has a cupric sulfide cathode and an electrolyte consisting of lithium perchlorate in a mixture of organic solvents (Fig 8) The cells use a crimped seal construction with a thin flat anode, a porous separator, and a pressed flat cathode all in a sandwich less than 5 mm thick The separator allows electrolytes to pass freely but prevents diffusion of cathode material toward the anode A polypropylene gasket seal is designed to be impermeable to the electrolyte but it is gas permeable * Electrolyte conductivity is quite high so that cell resistance remains low throughout life Cell voltage remains near open circuit voltage for 90 per cent of total cell life Ultimately the voltage drops to a second lower value where it remains constant for the remaining time and the pacer continues to operate at a reduced pacing rate EOL is indicated by this rate drop, and it is estimated that ample time (approximately 1 year

*See footnote second column

*Hermeticity of a battery is neither a positive or a negative feature although it was long considered to be an asset Some lithium must be hermetically sealed because the electrolytes such as thionyl chloride or iodine if released from the cell are corrosive to the electronic circuit and toxic to the tissues The thionyl chloride cell has a double internal seal one around the cell and the battery is contained in another hermetic compartment Other cells (Cordis/DuPont and SAFT) need not be hermetically sealed because the electrolytes in reaction products are non corrosive and non toxic The cases of these cells are crimped and are not truly hermetic Nevertheless most present lithium powered pulse generators have an *external* hermetic seal (Hermeticity is technically defined as a leak rate of less than 1 × 10 standard cubic centimeters of helium per second per atmosphere)

of 10 per cent of total battery life) will remain for pacer replacement.

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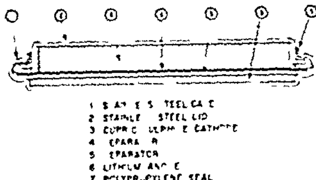


Fig. 8. Diagram of lithium cupric sulfide cell (Cordis DuPont)

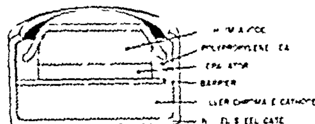


Fig. 9. Diagram of lithium silver chromate cell (SAFT)

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Power source	*Per cent of total*	*Projected new pacers for 1977**
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Regular output	18%	
Reduced output	3%	
Lithium	59%	80%
Nuclear	15%	10%
Rechargeable	<0.%	0%

*These figures represent the personal preferences (and prejudices) of the Hospital Pacemaker Center.

Medical Center to provide the cumulative survival curves seen in Fig. 10. Similar results have been reported by others.[19,20] There have been more than 20,000 lithium implants in the past five years and so far there have been no battery failures. Component failures have been rare, occurring at a rate of less than 0.3 per cent per year.

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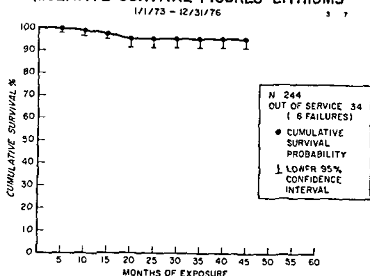


Fig 10 Cumulative survival curve of lithium powered pul e generator implanted at the Newark Beth Israel Medical Center

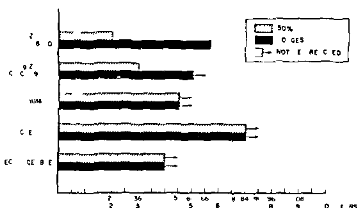


Fig 11 Experience to date with standard mercury/zinc powered cells and pulse generators powered by lithium rechargeable thermonuclear cells The approximate 50 per cent failure time is indicated although that time has not yet been reached in any of the long life cells (Data compiled largely from registry)

each with individual merits The more recent versions have become smaller without losing longevity because the energy density and effi ciency of the cell have increased and internal self discharge losses have decreased Still better cells are under investigation In the future it will be preferable to describe pulse generators by *make* and *model* number and to discontinue the generic term of lithium pacemaker A compar ison of the known experience with various types of generic pacemakers is shown in Fig 11

Nuclear pacemakers

Radioisotopic energy for a pacemaker battery has received much attention over the years

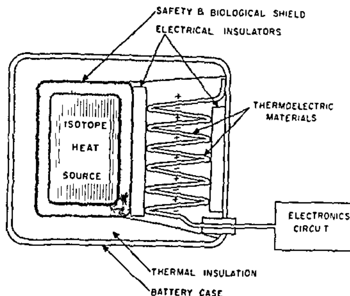


Fig 12 Diagram of mode of action of radioisotope powered cell (Pu) (From Parsonnet V The nuclear pacemaker in perspective *in* New Horizons in Cardiovascular Practice Russek H I ed Baltimore 1973 University Park Press pp 473 483 Reproduced by permission of the publishers)

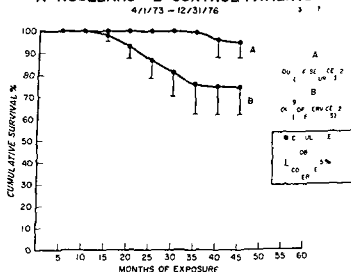


Fig 13 Cumulative survival curve for 112 nuclear pace makers and 94 controls implanted since April 1973 at the *Newark Beth Israel Medical Center*

because it was the first truly new and different implantable power source Its use also provoked much controversy because of concern for the patient s safety and for the environment These fears have been shown to be groundless First implanted in dogs in 1969 and in humans in 1970 nuclear pacemakers have now been released for general use in the United States under limited licensure by the NRC

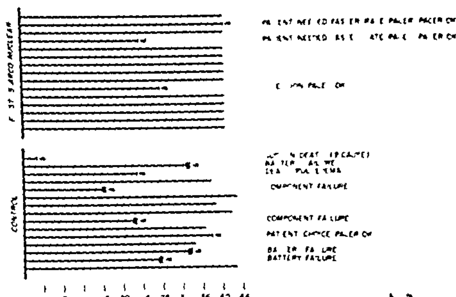


Fig. 14. Forty month follow up of first 15 nuclear pacemakers (ARCO) and matched non nuclear control implanted at the Newark Beth Israel Medical Center

Of the two systems for converting radioisotopic energy to electrical energy namely betavoltaic and thermoelectric only the latter remains in clinical use. The thermoelectric system uses the heat produced by the isotope ²³⁸Pu and converts it into electrical power (Fig. 12). The isotope acts only as a heat source, the heat passes through the energy conversion materials (a thermopile) to produce an electrical potential by the Seebeck or thermocouple effect. The battery output passes continuously through the electrical circuit in the same way as current from a chemical cell. Because the isotope is only a heat source it can be encapsulated independently with a metallic barrier that serves also as a radiation barrier. Thermal insulators are used to induce the maximum amount of heat to flow through the thermopile. The first pacemaker developed originally by the Numec Corp., now ARCO Medical, uses a metallic thermopile, the wires of which are connected in a multi redundant arrangement for maximum reliability. All other pacemakers using plutonium power use bismuth telluride as the conversion material.

Bismuth telluride is considerably less ductile than a metallic thermopile and has a greater potential for fracture but it has been adequately protected against shock by all manufacturers. The chief appeal of this material is its superior efficiency of thermal conversion which permits a lower isotope fuel supply. This advantage is partially offset, however, by a lower voltage output than that obtained from the metallic system; therefore in a pulse generator a DC/DC voltage converter is required. The resultant batteries of the two systems, one with and one without the converter, are ultimately similar in size and efficiency.

Plutonium 238 is primarily an alpha emitter with a half life of 86.4 years, and a relatively low radiation dose rate when encapsulated. The yearly whole body radiation effect is in the order of magnitude of one annual diagnostic fluoroscopy or the average radiation background in the United States. Nuclear pulse generators have been designed to last 10 to 20 years.

Clinical experience

Since 1970 more than 2,308 nuclear pacemakers of six companies have been implanted throughout the world (Table IV). There has not been a single known battery failure. About 4 per cent of the units are out of service for other reasons (exclusive of deaths) such as those shown in Table V.

Our experience with 112 nuclear implants at the Newark Beth Israel Medical Center since April 1973 has been similarly good. The average followup of these units is 21.3 months with but one pulse generator failure due to a faulty component. A cumulative survival curve of 112 cases, as compared to a set of 94 non randomized controls, is shown in Fig. 13. A comparison of the first 15

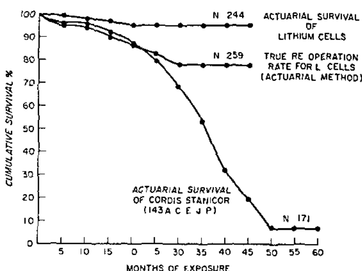


Fig 15 Actuarial data on lithium pacemakers taking into account all reoperations

units to a *series of matched controls implanted* almost four years ago is beginning to show the *impact of the over all improvement* in quality and reliability of nuclear units over mercury/zinc powered pacemakers (Fig 14)

The radioisotopic battery was designed to last 10 years with 95 per cent confidence limits So far seven years after the first implant, there is every reason to believe that this objective will be achieved and that a pulse generator longevity of 20 to 30 years is a reasonable expectation

Discussion

Note that all causes of reoperation are not reflected in the cumulative survival curve but *only pulse generator failure* True reoperation rates for lithium powered pacemakers may be expressed better in Fig 15 in which *all* causes for reoperation have been taken into account It is important therefore to distinguish between *pulse generator* survival, and *pacemaker system* surviv al because about 20 per cent of reoperations are due to causes other than failure of the pulse generator (This will be discussed further in a succeeding article) There is a tendency to think of the modern pacemaker in terms of the power source and to forget that developments in elec tronic and materials technology occurred concur rently *Actually lithium cells do not provide* great increments in power over the earlier mercu ry-zinc batteries in fact the gravimetric energy density, expressed in ampere hours per gram is *within the same order of magnitude* although volumetric density is somewhat greater

The virtue of the lithium cells lies in the *other* qualities of the cell particularly hermeticity or near hermeticity which permits secure *isolation* of the cell from the electronics and from the hostile seawater environment of the body *This isola* tion alone has eliminated many cases of pulse generator failure and has extended average pacer life But it is other features of the lithium pace makers and for that matter all other pacemakers manufactured today, that should really be cred ited for the extended pulse generator life New circuit configurations drain less current from the battery, microcircuits enclosed in hermetically sealed cans reduce the likelihood of component failure small electrodes reduce the amount of *current required to stimulate the heart* and there

Table III Nuclear pacemakers commercially available—1977

Medtronic—Medtronic Inc Minneapolis Minn
Coratomic—Coratomic Inc Indiana Pa
ARCO—ARCO Medical Products Leechburg Pa
Cordis—Cordis Corp Miami Fla

Table IV Nuclear pacemakers—World wide experience (12/31/76)*

Type	*Total im planted*	*USA*	*Else where*	*In service*	*Longest follow up (months)*
Alcatel Medtronic	1531	495	1036	1392	81
ARCO	126	124	2	103	45
Biotronik Betacel	246+	55	(12/31/75) 191 No 1976 data	?	48
Coratomic	261	261	–	243	28
Cordis	94	91	3	93	26
Total	2258+	1026	1232+	1831+	
Devices—					
Harwell ≅	100 (1971)				
Siemens	0				
	2358+				

Includes only models available in U S
? = *Data incomplete*

Table V Nuclear pacers—2258+ World wide Reasons for out of service (12/31/76)

Type	Number implanted	Out of service	Deaths	Other reasons
Alcatel-Medtronic	1,31	139	67	38 infection/erosion 22 lead problems 6 other complications 6 pacemaker failures
ARCO	179	23	7	16 infection/erosion competition (VOO) 3 lead problems 1 elective replacement not pacer related 3 component 2 patient required faster rate pacer
Betacel Biotronik		*	*	component (U.S.) ? information outside U.S. is unavailable
Coratomic	401	18	6	12 component 8 lead problems insufficient R wave amplitude 2 replaced during electrode replacement procedure
Cordis	94	1	1	0
Total	2258+	181+	81+	100+

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the electrical output for each impulse is reduced (or can be adjusted downward by external non invasive programming) and the electrode connectors and welds are of superior design eliminating still other causes of pacemaker system failure

So far there has been no reported case of lithium or nuclear battery failure Of course it does not follow that the need for continued pacemaker follow up has been reduced Experience tells us that there is a vast difference between the estimates of pulse generator longevity and eventual pacemaker system performance Battery failure in general accounts for only half of pacemaker reoperations therefore monitoring must continue in order to detect all the other problems that may occur Third party carriers fail to understand the distinction between the battery and the other components of a pacemaker and therefore have tried to reduce the approved schedule of routine follow ups If future reliability does live up to expectations some changes in schedule will be reasonable but at present such a change is premature

The relative merits of the various power sources for implantable pacemakers have been discussed with regard to technology and clinical experience A subsequent article will take up the problems of indications selection of the proper pacemaker and safety

The authors wish to acknowledge the contribution and advice of George H Myers, Ph.D Peter Jacobson of Coratomic and Wilson Greatbatch of Wilson Greatbatch Ltd. Valuable information has also been supplied by David Morley of ARCO Medical Products Lawrence Shearon of Medtronic and Peter Tarjan of Cordis. We also thank Drs. Lawrence Gilbert and I Richard Zucker for their collaboration in the clinical phases of this report.

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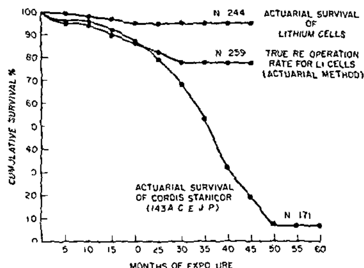


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The digoxin concentration before and after the fact

Despite warnings about improper use of blood concentration of drugs, physicians persist in regarding them as a diagnostic guide to drug effects on the body (i.e., pharmacodynamics) instead of regarding them primarily as a guide to the effect of the body on the drug (i.e., pharmacokinetics). What are the factors which govern the relationship between the dose of a drug and its effect? They may be divided between factors affecting the relation between dose and blood concentration and factors affecting the relation between blood concentration and effect. The first group of factors can be studied by use of pharmacokinetic principles and the results can be translated into quantitative decisions to improve the chances of reaching a desired blood concentration. The variables relating blood concentration and effect are far more difficult to quantify and even more difficult to alter. The effect of a given digoxin concentration on heart rate depends on factors such as the ratio of intracellular to extracellular potassium, the severity and nature of cardiac disease, the presence of coexisting disease (e.g., thyrotoxicosis) and, of course, biological variation in the response of the digoxin receptor.

If the effect of a drug is somewhat unpredictably related to its plasma concentration, why would anyone want to know or measure the concentration? Aside from the important use of the drug concentration to investigate abnormal pharmacokinetics, the answer is that the concentration is often related better to the effect than the dose is. That is, a group of patients, all with the same drug concentration, will show effects more similar to each other than will a group of patients all receiving the same dose. When is this property useful? Only when the drug's effects themselves cannot easily be used to adjust dosage. This can be true for digoxin, for example, because inotropism is difficult to measure; it can be true for phenytoin because the "absence of seizures" is difficult to quantitate. In such circumstances the drug concentration is used as an intermediate therapeutic endpoint, just as the prothrombin time is used as an intermediate endpoint for anticoagulants. Concentrations are measured periodically to assess individual pharmacokinetics so that doses can be adjusted more accurately. The important point is that this use is prospective: the intermediate endpoint is regulated so as to make *future* efficacy probable and *future* toxicity improbable. The endpoint itself is periodically adjusted according to whether or not the ultimately desired effects are achieved.

If a patient of yours on anticoagulants had a prothrombin time of 30 seconds (at the "upper limit" of the therapeutic range) but had melena, you wouldn't conclude that the anticoagulants had nothing to do with the bleeding. The same, of course, is true for "non toxic" drug concentrations. This situation is different from the prospective one because here the argument is retrospective, about past events, not future ones. Surprisingly, this makes all the difference.

Yet how often is the serum digoxin concentration used as a pharmacodynamic axe instead of a pharmacokinetic scalpel! Its use as an axe to separate patients into those with or without digoxin toxicity has been recently reviewed and, to judge from ensuing editorials and extensive correspondence, many physicians are disappointed by the bluntness of the axe's edge. How can a test which has a false positive rate as low as 10 per cent fail so consistently when it is needed most? The answer lies in the retrospective vs. prospective breakdown. The theoretical basis for this has been reviewed on several occasions for a medical audience, but a wider appreciation of these principles may be gained from the following common clinical scenes.

Patient A. A [illegible]-year-old man taking 0.5 mg digoxin and 80 mg furosemide per day. He stopped taking his potassium supplements because he thought they were responsible for his feeling nauseated. His ECG shows an atrial tachycardia with block and his BUN is [illegible]0 mg per cent.

Physician's impression: "Obvious digoxin toxicity."

Reason for requesting digoxin concentration: "Let's see just how toxic this man is."

Reaction to "non toxic" test result: "'Non toxic'! Impossible. Ingelfinger and Goldman are quite right—this test is useless."

Feelings about the test: "If the test doesn't give the right answer when the diagnosis is obvious, how can it ever be right?"

Patient B. A [illegible]5-year-old woman taking 0.25 mg digoxin per day. She has lost her appetite and has been feeling unwell. BUN and electrolytes are normal. Pulse rate is 65.

Physician's impression: "Probably digoxin toxicity."

Reasoning for requesting digoxin concentration: "Let's just be sure it's the digoxin. Her symptoms could be due to something else."

Reaction to "non toxic" test result: "It's a good thing I checked the digoxin level. Obviously something else is amiss. Let's get an upper GI series and a gastroscopy in case she has gastric cancer."

Feelings about the test: "A very useful test. Helpful in these uncertain situations when signs and symptoms are so nonspecific."

Patient C. A 45-year-old woman with mitral stenosis and atrial fibrillation. She has been taking the same dose of 0.25 mg/day for two years. She is attending clinic for routine follow up and has no clinical features of toxicity.

Physician's impression: "Doing well—no obvious problems."

In three patients subsequent operation revealed an adrenal adenoma The remaining two patients were not operated upon although quadric analysis[1] clearly predicted an adrenal adenoma in each case Plasma vasopressin levels ranged from 3 5 to 6 5 pg /ml (4 7 ± 0 6 mean ± S E M) while plasma osmolality was not significantly higher than in normal subjects Vasopressin values are similar to those seen in benign essential hypertension again lower than normal although the number of patients is rather small for comparison It is perhaps not surprising that low vasopressin levels would be seen in a condition characterized by an expanded plasma volume[12]

On the evidence available therefore there is little to suggest a role for vasopressin in hypertension in man

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Of hemiblock propaganda

Patients with horizontally positioned hearts or even with left ventricular hypertrophy and/or dilatation are not considered to have left axis deviation any more They now all have hemiblock The evidence for left axis deviation (LAD) established over the many years following considerable clinical research is no longer interpreted as LAD but rather as

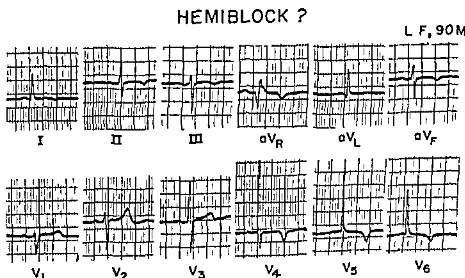


Fig 1 Standard 12 lead ECG which was erroneously interpreted as showing evidence of left anterior hemiblock

hemiblock." There are criteria for block of the anterior bifurcation of the left bundle branch (LBB) but they are not based merely on the presence of LAD. In fact, unless the LAD can be shown to develop suddenly or to disappear suddenly (within the interval of one heart beat) the presence of hemiblock is almost impossible even though right bundle branch block may be present simultaneously. Fig. 1 shows an electrocardiogram (ECG) erroneously interpreted as reflecting "hemiblock" (block of the anterior bifurcation of the main left bundle branch). The ECG must be interpreted properly because some physicians consider hemiblock to indicate a grave prognosis (and even this is yet to be fully established) and to indicate the immediate need for a pacemaker (which is not necessarily so on the basis of hemiblock alone). An astute physician treats the patient, not the ECG interpretation of hemiblock."

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Methods for measuring plasma or blood glucose in the clinic: A short review

The growth and development of biochemistry in the past 70 years has given clinicians access to a wide range of chemical tests, many of which have become an integral component of clinical medicine. Chemical tests are commonly used in the initial investigation of patients, during the treatment of acute medical disorders, and as an index of the course of a disease. Blood or plasma glucose measurements are required as urgent analyses, for the diagnosis of hyperglycemia and hypoglycemia, and for monitoring the treatment of patients with acute diabetic metabolic decompensation.

The measurement of blood sugar concentration became a practical proposition for the first time with the development in 1920 of a relatively sensitive reduction method by Folin and Wu, followed shortly thereafter by the reducing sugar methods of Folin and of Nelson. From a clinical point of view blood sugar measurements assumed major importance when schedules of treatment for diabetes were developed after the classical studies of Banting and Best, which led to the discovery of insulin. Reducing sugar methods are still used in some clinical laboratories. These methods all have the disadvantage of a lack of specificity for glucose due to the presence in blood of small quantities of non-glucose reducing substances such as lactose, galactose, glutathione, and ascorbic acid. A variety of drugs including salicylates may also interfere with the reaction. Reducing methods tend to provide falsely high values for blood glucose concentration.

An important advance in glucose methodology came from the discovery of an enzyme in extracts of *Aspergillus niger* which catalyzed the oxidation of glucose to form gluconic acid. This enzyme, now called glucose oxidase, is the basis of the most widely used enzymic methods for measuring glucose concentration.

Early methods using glucose oxidase were both cumbersome and tedious since they required measurement of oxygen uptake or the loss of reducing substances during the course of the reaction. Clearly these methods were quite unsuitable for use outside the laboratory environment. In order to use the enzyme as a component of a glucose measuring system, it is necessary to link its activity with a measurable end point. In 1956 Teller and Keston described more convenient methods for measuring glucose concentration by the sequence of reactions shown below.

Table I

Glucose	Glucose oxidase ⟶	Gluconolactone + Hydrogen peroxide		
Hydrogen peroxide	+ Reduced chromogen	Peroxidase ⟶	Oxidized chromogen	+ Water

The important link between the amount of glucose present in this system and the oxidation of the colorless reduced chromogen is provided by incorporating the second enzyme, peroxidase, into the reaction mixture. There is a molar relationship between the amount of glucose converted to gluconolactone and the amount of colored oxidised chromogen formed. This series of reactions provides the basis of a wide range of methods, some of which are suitable for use outside the laboratory environment.

Many different types of chromogen have been introduced and an important disadvantage of some of these is their potentially carcinogenic properties. Examples of carcinogens still in common use are o-dianisidine and o-tolidine (the use of benzidine as a chromogen has been completely abandoned).

Increased specificity, an advantage gained from the use of glucose oxidase, has also been obtained from the use of other enzyme preparations including hexokinase. Methods based on the hexokinase enzyme and which are suitable for use by skilled laboratory staff have not been generally accepted for use by the clinician or nursing staff largely because of the technical difficulty associated with measurements in the ultraviolet spectrum.

Wet methods based on the reducing sugar technique have been used for "glucose" measurement in the clinic. These have been abandoned because they are technically demanding, time-consuming, and relatively non-specific and have been replaced by the glucose oxidase method shown above. In order to make this convenient to use, the reagents are

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Of hemiblock propaganda

Patients with horizontally positioned hearts or even with left ventricular hypertrophy and/or dilatation are not considered to have left axis deviation any more They now all have hemiblock The evidence for left axis deviation (LAD) established over the many years following considerable clin ical research is no longer interpreted as LAD but rather as

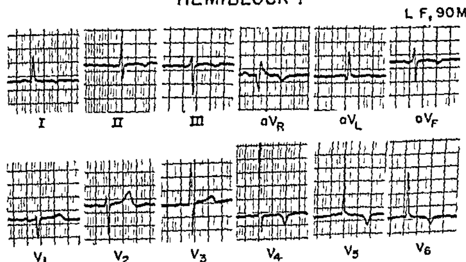


Fig 1 Standard 12 lead ECG which was erroneously interpreted as showing evidence of left anterior hemiblock

measurement the impregnated area of a test strip is covered with a drop of blood or plasma. After exactly 60 seconds the strip is carefully blotted with cotton wool and 60 seconds later the developed strip is inserted into the meter and a reading is made. The appropriate side of the scale is used depending on whether plasma or whole blood is being analyzed. The Reflomat System gives a linear response throughout its working range. A comparison between results obtained with the system and a glucose oxidase based AutoAnalyzer method is shown in Fig 2. In our hands a coefficient of variation of 3.1 per cent was achieved.

With both of these systems it is essential to allow the test strip to reach room temperature before use, as enzyme based reactions are temperature-dependent. Falsely low results may occur if strips are used straight from the refrigerator. In the busy laboratory or casualty department the meters may be left switched on for long periods of time, thus eliminating the need for a warming up period before use. Provided initial calibration has been performed correctly, recalibration appears to be unnecessary for periods up to three hours. To reduce the risk of errors, however, it is wise to check calibration before each batch of analyses.

Clinicians now have the means by which rapid, accurate and precise measurements of blood or plasma glucose concentration may be made in the emergency situation. The limited ranges of both systems described, however, limit their use in the treatment of hyperglycemic coma and in assessing patients suspected of being hypoglycemic. The Reflomat System does not measure glucose concentrations below 50 mg/100 ml and, although the meter on the Eyetone System extends as low as 10 mg/100 ml, both the accuracy and precision of results less than 40 mg/100 ml are dependent on the packed cell volume of the blood sample and on the sensitivity of individual test strips. A critical assessment of the Eyetone System at low glucose concentrations is needed.

An important criticism of many side room methods is that they are often performed in the absence of adequate quality control. No formal quality control facility is provided with Dextrostix. The Reflomat System, however, includes a vial of glucose quality control solution which enables the operator to assess the function of the system each time he performs an analysis. While the standards of performance described here can be obtained under ideal conditions, in practice it has become clear that systems of these types must only be operated after a period of staff training and that, without continuing supervision and monitoring of performance, the quality of performance may deteriorate markedly. Wide variations in accuracy may still arise between individuals using the same apparatus. It is most important, therefore, that regular independent checks on performance are maintained. Only with a combination of scrupulous care by the analyst and regular independent checks can confidence be placed in the results obtained with these systems.

Recent studies in our laboratory have highlighted a more sinister source of error which may occur when using test strip methods for measuring glucose concentrations, namely, the incorporation of sodium fluoride as a preservative. The presence of fluoride ions in the concentrations normally found in commercially produced tubes for the collection of blood glucose samples (47 mmol/L) will lead to low results with both the Reflomat and Eyetone systems (Fig 3). This appears to be due to inhibition of the relatively small amount of glucose oxidase present in the reagent test strips. Fresh blood obtained by finger prick or blood containing sodium heparinate as anticoagulant should therefore be used with both of these reagent test strip methods.

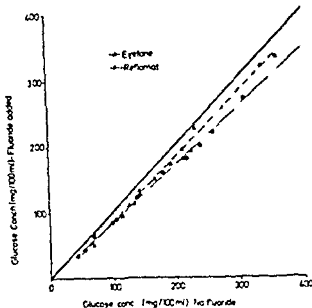


Fig 3. Comparison of the effect of fluoride ions on plasma glucose measurements obtained with the Eyetone and Reflomat systems. Venous blood was collected into heparin anticoagulant. Fluoride ions (47 mmol/L) were added to one half of the plasma sample and glucose assays were performed on the fluoridated and non fluoridated samples. *The solid line represents the line of perfect identity.*

It is commonly found that progress in patient care and in laboratory techniques proceed together. Advance in the understanding of factors affecting glucose metabolism and in the care of conditions resulting from abnormal glucose metabolism have led to pressure on the development of rapid methods for measurement of glucose concentration in blood or plasma. These methods have been modified for use by medical or nursing staff to enable them to perform the assays in the clinic or hospital ward without a requirement for the extensive training needed by professional laboratory staff. This article describes the performance of two systems developed for measuring blood or plasma glucose concentrations under these circumstances.

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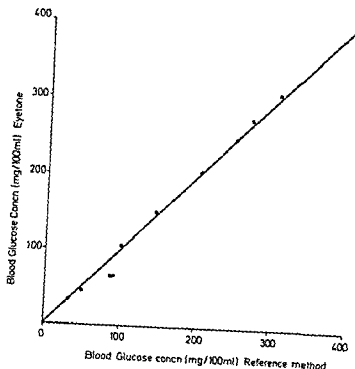


Fig 1 Comparison of Dextrostix/Eyetone system and AutoAnalyzer (reference) glucose oxidase method Venous blood samples were collected and a portion for the reference method was added to fluoride/oxalate anticoagulant *The solid line on the graph* represents a line of perfect identity between the methods

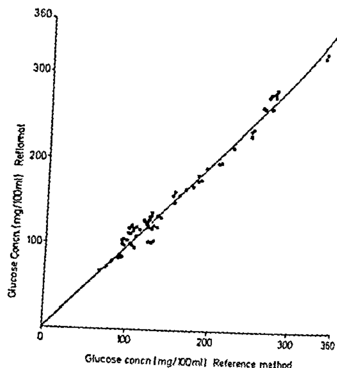


Fig 2 Comparison of the Reflotest Glucose/Reflomat system and AutoAnalyzer (reference) glucose oxidase method Venous blood samples were collected and a portion for analysis by the reference method was added to fluoride/oxalate anticoagulant *The solid line* represents a line of perfect identity between the methods

impregnated on to absorbent pads attached to one end of a plastic strip These dry strip methods reduce the risk to the user of exposure to carcinogenic chromogens (σ tolidine) and make it unnecessary to hold supplies of relatively unstable liquid reagents in the clinic Reagent test strip methods for measuring blood glucose concentration were first developed in 1964

Two methods for measuring glucose concentrations will be discussed The Dextrostix Eyetone system* is designed for use with whole blood while the Reflotest Glucose system† may be used for analysis of either whole blood or plasma glucose concentration

Dextrostix was the first reagent impregnated blood glucose test strip method to be introduced for use in the clinic by untrained personnel To perform the test a drop of blood is placed on the impregnated area of the strip and a stopwatch is started After exactly 60 seconds the blood is washed off with water and the color which has developed on the strip is compared by eye with a color chart provided If carefully performed this procedure is capable of producing a semi quantitative estimate of blood glucose concentration Owing to the method of comparison with a series of colored reference blocks each of which represents a range of glucose concentra tion results are discontinuous

In order to provide a continuous range of glucose concentra tions and to improve the accuracy of the results a reflectance meter was introduced in 1970 This in turn was superseded in 1973 by a more sophisticated meter the Eyetone Reflectance Meter In order to use this the Dextrostix Test strip is inserted after the 60 second color development period into the meter A brief warm up period is required between switching the meter on and calibration using the preset strips provided A result expressed in milligrams per 100 ml is then read from the analogue dial The working range of the meter is 0 5 to 22 mmol /L (10 to 400 mg /100 ml) A comparison of results obtained with this system and with a glucose oxidase based AutoAnalyzer method is shown in Fig 1 In our experience the precision obtained with the Eyetone Dextrostix system is approximately 5 per cent This precision was also obtained in an inter laboratory trial

While these standards of accuracy and precision can be obtained it is essential that careful instruction of users in the use of the system and regular checks of performance are carried out particularly as experience with the earlier Ames Reflectance Meter system revealed the ease with which misinterpretation of instructions can occur

Reflotest Glucose Strips accompanied by the Reflomat Reflectance Meter were introduced in 1974 This system is designed to permit the operator to measure either whole blood or plasma glucose concentration in a concentration range from 2 75 to 19 25 mmol /L (50 to 350 mg /100 ml)

Reflomat Glucose Strips come complete with preset calibra tion strips a scale calibrated on one side for plasma and on the other side for whole blood and a glucose control solution The control solution appears to be stable for up to 3 months if carefully stored at 4 C This latter feature is particularly important as it enables the operator to check that the system is working satisfactorily After allowing the meter to warm up it is adjusted using a calibration strip and the zero point is checked with a fresh reagent strip To perform a glucose

Ames Corporation Elkhart Ind
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Letters to the Editor

Exercise—hazard or health aid

To the Editor

The idea that one type of exercise is beneficial and another harmful may appear mystical to Dr Eskwith but there is scientific evidence this may be true

I refer you to Dr Joel Morganroth s report on two types of athleti heart the diastolic heart of the distance runner and the systolic heart of the weightlifter and shotputter

We distance runners naturally look on the diastolic heart as the one to ha e But then we do tend to be mystics

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What kind of evidence?

To the Editor

In the August 19 6 issue of the JOURNAL Eskwith in reply to a letter writes the following Circumstantial evidence no matter how strong has no place in scientific discipline and cannot be substituted for proof neither can anecdotal reports He considers his correspondent s contention that one type of exercise can be beneficial, another harmful too mystic a concept to be believable In this connection it may be useful to ask what kind of evidence *is* acceptable to science?

It is clear that data can be misinterpreted and medicine like any other branch of science provides ample scope for human error Equally clearly generalizations and hypotheses should be carefully scrutinized before they gain acceptance As there is only one basic faculty of human reasoning the scientist has no other mental equipment at his disposal than anyone else He differs only in the more disciplined use of this faculty imposed on him by more rigorous criteria of what constitutes acceptable evidence of validity

Generalizations based on a few examples to which the vogue term anecdotal presumably applies belong to the genus of statistics derived from an insufficient number of samples They can doubtless be sources of error An amusing example is cited by Gordon writing of a Russian report to the effect that the incidence of heart disease was higher among the staff of a Moscow Institute of Food than in an Institute of Geology

While on the subject of possible sources of error may I mention another example? This is the often ignored uncertainty when the results of animal trials are applied to human practice An example is the classic experiment in 1913 of Anitchkow and Chalatow who were the first to produce atheroma like lesions in cholesterol fed rabbits The source of error in this case is that some mammals, including man possess a mechanism regulating the absorption of dietary cholesterol, enabling them to reject excess intake undigested while some herbivores like rabbits, do not The presumable reason is that plants contain little cholesterol so that the ingestion of a quantity in excess of need is so unlikely for a herbivore under natural conditions that a mechanism capable of rejecting such excesses has no survival value for them The lack of this information in the earlier decades of the present century has led to the ill founded but widely accepted belief that excess cholesterol in the diet was the main cause of human atheroma

However it is possible to err in two directions. In science *insistence on too rigorous criteria* of validity can have a stifling effect Non-communicable diseases like cancer atheroma or multiple sclerosis, seldom oblige us by providing easily recognizable clues for their etiology and pathogenesis, so who is to provide those perfect incontrovertible scientifically acceptable hypotheses? Since beginnings have to be made somewhere most probably imperfect beginnings is it not the case of cutting our coats to fit our cloth? Insistence on perfection is likely to result in scientists refraining from attempting the impossible and keeping to data-collecting and fact finding

The worst example in this respect is cancer research with its flood of literature on experiments with inbred x ray irradiated, cortisone treated rats. Most of these experiments are probably irrelevant to any aspect of human cancer and most are probably of the nature of trying to find out how a motorcar worked by experimenting on it e g by drilling holes in its hood or by mixing chicken blood with its gasoline While such experiments are impeccably scientific in form they are utterly sterile and unproductive in practice Perhaps the best judgment on them to quote Gordon again seldom can so much have been written by so many and read by so few "

In my opinion the only practicable criterion of validity ever produced by science is that of consistency A deduction or generalization derived from one set of data is tentatively regarded valid if it is consistent with similar deductions or generalizations based on another set of data and is finally incorporated in the tenets of science unless later challenged by new observations This is how science does, in fact progress The progress may be halting and jerky but in the long run it is progress

Let us consider how all this applies to the subject of Dr Eskwith s letter In my opinion any evidence relevant to a problem is admissible and cannot be rejected by catchwords like circumstantial or anecdotal " The replier should take the trouble to explain why a thesis is unacceptable that is provide data which contradict it or with which the thesis is inconsistent

I do not agree that the proposition that some exercise can be beneficial other harmful is obviously wrong Sudden bursts of violent exercise could be harmful because they are likely to find any weakness of the circulatory system Sedentary life can conceivably be harmful because never used capillaries and arterioles may disappear which may mean the difference between death and survival in an emergency following the

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He underwent cardiac surgery on April 16, 19 3 The ventricular septal defect was repaired the ventricular aneurysm excised and the mitral valve was replaced He made a good recovery Since then he had another myocardial infarction and an episode of right ventricular failure He remains mild to moderately dyspneic but is able to carry on his normal activities.

Comments

This patient had cardiac catheterization primarily for surgical evaluation Surgical correction of ventricular septal defect and mitral regurgitation has been responsible for his long term survival. Right heart catheterization by Swan Ganz technique may be of value in the medical management of the patient but when mitral regurgitation is accompanied by ventricular septal defect its diagnostic value becomes limited The wedge and left atrial V waves approaching 50 mm Hg have been noted in patients with ventricular septal defect complicating myocardial infarction in the absence of mitral regurgitation. This was also shown in the patient who on the basis of cardiac catheterization without angiography initially was reported to have ventricular septal defect and mitral regurgitation complicating myocardial infarction but did not have mitral regurgitation on autopsy It appears that this is the longest surviving (years) patient with combined ventricular septal defect mitral regurgitation and ventricular aneurysm complicating myocardial infarction

(This patient was under the care of Doctors Richard S Crampton Joel P Schrank and Harry A Wellon. Jr at the University of Virginia Medical Center Charlottesville Virginia)

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Reply

To the Editor

Dr Zaidi should be congratulated on the diagnosis and management of their patient with myocardial infarction complicated by mitral regurgitation and rupture of the ventricular septum We had postulated that surgery might be helpful and Dr Zaidi in his case report demonstrated that indeed surgery was helpful and further emphasizes the need for recognition

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REFERENCE

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Revised data for 1970 ICHD Report

To the Editor

In his recent article in the AMERICAN HEART JOURNAL (81 87 19) Dr Lars Werko noted certain inconsistencies in the data from the national cooperative Pooling Project published in the Report on the Primary Prevention of the Atherosclerotic Diseases of the Inter Society Commission for Heart Disease Resources (ICHD) (*Circulation* 42 A55 1970) and elsewhere In the course of completing the data analyses for the Final Report on the Pooling Project (currently in press) all the analyses in the 19 0 Report were re-done It is a fact that there are inconsistencies in the earlier data overlooked by us heretofore and we are grateful to Dr Werko for detecting them Specifically of the several sets of data in the 1970 ICHD Report there are errors in Table IV in one of the four analyses in Fig 10 and one of the eight analyses in Fig 12.

Tables I to III below set forth the originally reported findings (*left*) and the corrected data (*right*) These corrected data are derived from the final data tape of the Pooling Project prepared many months after the original tape used in 1970 for the data analyses for the ICHD Report. Subsequent editing of this earlier tape resulted in small numerical differ

Table I Sudden death and acute mortality with first major coronary events men age 30-59 at entry Pooling Project* ten year experience

Event	*1970 ICHD Report (Table IV)* No of events	*1970 ICHD Report (Table IV)* Proportion per 1 000	*Final data* No of events	*Final data* Proportion per 1 000
All first major coronary events non fatal and fatal	501	1 000 0	585	1 000 0
Sudden death	1 3	245 6	156	266
All acute deaths with first events	165	379 3	25	439 3
Number of men	7 594		7 545	

*The five studies pooled for these analyses were Albany Civil Servant Chicago Peoples Gas Co Chicago Western Electric Co Framingham Community and Minnesota Business and Professional Men studies

occlusion of an artery in the coronary circulation Moderate regular exercise may steer a median course between the two evils

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Reply

To the Editor

I now find myself answering letters written to the reply of my original communication to your JOURNAL In reference to Doctor Sheehan s letter perhaps long distance runners have a lower mortality from heart disease perhaps not They form a very small group Regardless of what their mortality is I can t see the general population getting up every morning and running twenty miles before reporting to work I don t think we should be too sanguine about this small group of people until more data have been compiled on them

Doctor Seely s letter is most interesting To my mind objective evidence in connection with atherosclerotic heart disease would be the application of a remedy which by itself produces a sharp and sustained reduction in mortality from heart disease An example of such objective evidence would be the mortality from subacute bacterial endocarditis prior to the use of penicillin therapy and afterwards Koch s Postulates still remain excellent guidelines for determining what objective criteria are It is apparently not considered stylish to read them anymore but I think we all should for they are as valid today as when they were originally written These furnish a good skeleton on which to construct any experiment that would have in mind the reduction of heart disease

Naturally as a writer even of a letter I have been very pleased at the response my original note has elicited Ventilation of controversy particularly in areas that are themselves controversial is always beneficial and stimulating

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The simultaneous occurrence of a ventricular septal defect and mitral insufficiency after myocardial infarction

To the Editor

It is of interest to note the rarity of simultaneous occurrence of ventricular septal defect and mitral regurgitation complicating myocardial infarction Doctors Gowda Loh and Roberts (AM HEART J 92 234 1976) remarked it is possible that surgery may be helpful when both lesions are present if recovery is possible for 2 to 3 weeks The following report demonstrates the success of surgery in such a case

Case report

A 61 year old white male was admitted to the coronary care unit of the V A Hospital Salem Va on April 2 1974 with the complaints of shortness of breath and ankle swelling He had been in his usual good health until two weeks prior to his admission when he developed vague chest pain and shortness of breath He consulted his family physician who prescribed some medicine but his symptoms continued to get worse and he had shortness of breath on mild activity orthopnea paroxysmal nocturnal dyspnea and swelling of his legs at the time of admission to the V A Hospital He smoked one pack of cigarettes per day and had some cough and mild dyspnea of effort in the past He did not have hypertension diabetes mellitus or angina pectoris His only previous admission to the hospital was in 1973 for bunionectomy

Physical examination revealed an ill looking man in respiratory discomfort His pulse was 100 per minute in regular rhythm Blood pressure was 95/50 mm Hg The neck veins were distended up to the angle of jaw with prominent V waves at 45 degrees inclination The point of maximal impulse of the heart was in the anterior axillary line in the fifth left intercostal space (LICS) No thrills were palpable There was a summation gallop pericardial friction rub and 3/6 pansystolic murmur The murmur was heard maximally in the fourth LICS along the parasternal border but radiated to the apex and the axilla Bibasilar rales were present up to the angle of the scapulae The liver was tender and was enlarged two fingerbreadths below the costal margin There was pitting edema of the lower legs and sacral area X ray of the chest showed cardiomegaly congestion of pulmonary vessels and left ventricular failure The electrocardiogram revealed regular sinus rhythm with Q wave ST elevation and T wave inversion in Leads 2 3 aVF and T wave inversion in Leads V_6 Laboratory findings were SGOT 345 units SLDH 1096 units and CPK 21 units Hematocrit was 37 per cent and white blood cell count 7800/mm He was treated with intravenous furosemide salt and fluid restriction and digoxin He had a good diuretic response and had subjective and objective improvement but 36 hours after admission he became cyanotic and had no palpable pulses He remained in sinus rhythm Cardiopulmonary resuscitation was immediately initiated and pericardiocentesis was attempted but did not yield any fluid Norepinephrine infusion raised the systolic blood pressure to 100 mm Hg and one hour later he was able to maintain blood pressure on his own He was transferred to the University of Virginia Medical Center Charlottesville Virginia Cardiac catheterization and coronary angiography were performed These showed elevated right atrial pressure with a waves of 11 v waves of 12 and a mean pressure of 9 mm Hg Right ventricular and pulmonary artery pressures were 40/11 and 40/16 mm Hg respectively Pulmonary capillary wedge pressure was also elevated and showed a and v waves of 16 and 21 mm Hg There was a positive hydrogen curve in the pulmonary artery Pulmonary to systemic blood flow ratio was 1 3 and a left to right shunt of 0 64 L/min/M^2 Left ventricular end diastolic pressure was elevated at 22 mm Hg Left ventricular angiography showed 2 to 3+ mitral regurgitation akinesis of a large portion of inferior wall and a discreet inferior wall aneurysm just beneath the posterior medial papillary muscle Right coronary artery (RCA) cineangiography revealed the RCA to be the dominant coronary artery with complete occlusion in its proximal portion Both left anterior descending and left circumflex coronary arteries showed 50 per cent occlusion with poor distal vessels The next day he developed Mobitz II heart block and a temporary transvenous pacemaker was inserted

Book reviews

1976 Year Book of Cardiology Edited by W. Proctor Harvey M.D. Walter M. Kirkendall, M.D. John W. Kirklin M.D. Alexander S. Nadas, M.D. Oglesby Paul M.D. and Edmund H. Sonnenblick M.D. Chicago 1976 Year Book Medical Publishers Inc 506 pages.

The Year Book of Cardiology for 1976 contains abstracts of selected reports in cardiology for the convenience of the busy physician. Even though the reports are highly selected by the editors and their respective assistants, the reader has an opportunity to review rapidly some of the studies published in cardiology in recent months. The abstracts are not critically reviewed by the contributors. They reflect the findings and opinions of the authors of the original publications. The comments of the contributors of each abstract are extremely valuable and should be appreciated by readers who failed to study the original publications closely. This is a very good Year Book and all cardiologists will find owning and reading it extremely profitable.

An Atlas of Noninvasive Techniques By Aldo A. Luisada M.D. Gloria L. Perez M.D. and Pachalla K. Bhat M.D. Springfield Ill., 1976, Charles C Thomas, Publisher 5 8 pages Price $34.50

This atlas consists of 2?1 illustrations of non invasive recordings of cardiac hemodynamic phenomena with a fairly detailed legend of interpretations. The recordings are excellent and the interpretations are clear. The simultaneous recordings include tracings of common problems in cardiology such as heart sounds, carotid artery pulsations, electrocardiograms, jugular vein pulsations, echocardiograms, cardiac apex pulsations and others. The atlas is a good one which should assist residents and fellows training in cardiology in learning the interpretation and application of these tracings. Beginners will find it profitable to own this atlas and learn how these tracings reflect normal and abnormal cardiac disease states. This is a good addition to the literature in cardiology.

CRC Immune RNA. Edited by E. J. Cohen Cleveland 197? CRC Press, Inc., 114 pages Price $?7.?0

The book edited by Cohen consists of little more than 100 pages which succinctly summarize the role of RNA in immunology. The advances in immunology in recent years have been explosive by comparison with the distant past. With the interest in immunological problems in medicine and cardiovascular diseases, a better knowledge of the role of RNA complexes in this aspect of molecular biology should assist all physicians including cardiologists in understanding many diseases they treat. The five papers which constitute this publication summarize very well the problems related to RNA immunology. The interest in organ transplantation and immunosuppressant therapy renders it mandatory that physicians learn and know the language and the fundamental concepts of immunology. This includes the role of RNA and its various components and complexes in diseases states. This is a very good book and worth owning for reference.

Introduction to Echocardiography By Ian C. McDonald Springfield Ill 1976 Charles C Thomas Publishers, 2?? pages. Price $?? ?0

McDonald has added another good book to the many appearing recently on echocardiography. The book is intended for beginners. It is well written and includes a brief introduction to the physics of sound, the principles of the recorder and recording, as well as the role of echocardiography in clinical practice. The illustrations are good and the bibliography is grouped in accordance with the disease and anatomic structure under study. This is quite convenient for the reader. It will help all physicians who interpret and record echocardiograms. This is one of the best books available today on the subject for beginners. It is highly recommended.

Table II Major risk factor combinations at entry and 10 year incidence of first major coronary events, men age 30 59 at entry, Pooling Project

Risk factor status at entry	1970 ICHD Report (Fig 10 lower)			Final data		
	No of men	No of events	Rate per 1 000†	No of men	No of events	Rate per 1 000†
None of 3	1 249	28	20	1 246	32	23
Cigarette smoking (S) only	2 018	97	45	2 021	120	54
C or H only	1 302	74	52	1 293	82	54
(S + C) or (S + H)	1 794	167	92	1 790	195	103
(C + H)	384	31	85	381	37	92
All 3	595	82	171	597	95	189
All with data on 3 risk factors				7 328	561	72
Men with missing data on 1 or more risk factors				217	24	98
All men				7 545	585	72

Definitions of the 3 major risk factors and their symbols were Hypercholesterolemia (C)—≥ 250 mg /dl Elevated blood pressure (H)—diastolic pressure ≥ 90 mm Hg Cigarette smoking (S)—any current use of cigarettes at entry
†All rates were age adjusted by 10 year age groups to the U S white male population 1960

Table III Major risk factor combinations at entry and 10 year incidence of first major coronary events men age 30 59 at entry, Pooling Project

Risk factor status at entry	1970 ICHD Report (Fig 12)			Final data		
	No of men	No of events	Rate per 1 000†	No of men	No of events	Rate per 1 000†
None of 3	1 249	28	20	1 246	32	23
Any 1 only of 3	3 320	171	48	3 314	202	54
Any 2 only of 3	2 178	198	90	2 171	232	100
All 3	595	82	171	597	95	189
All with data on 3 risk factors				7 328	561	72
Men with missing data on 1 or more risk factors				217	24	98
All men				7 545	585	72

Definitions of the 3 major risk factors were Hypercholesterolemia—≥ 250 mg /dl Elevated blood pressure—diastolic pressure ≥ 90 mm Hg Cigarette smoking—any current use of cigarettes at entry
†All rates were age adjusted by 10 year age groups to the U S White Male population 1960

ences in the numbers of men in the denominators and in the number of men with events as indicated in the numerators These small differences are unrelated to the inconsistencies noted by Dr Werko The remaining Pooling Project data on risk factors in the 1970 ICHD Report contain no analytical errors

The final data show even higher percentages than before for the proportion of first major coronary events that terminated fatally suddenly or otherwise (Table I) Therefore the point made in the 1970 Report is reinforced i e a high percentage of first major coronary events manifest themselves as sudden death (death within three hours of onset of symptoms) or terminate fatally during the course of this first acute event

The final data show only small changes in the originally reported findings on the strong relationship between various combinations of risk factors and incidence of first major coronary events (Tables II and III)

This letter does not deal with other aspects of Dr Werko s paper Many of the judgments and critiques set forth there certainly merit further discussion

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Book reviews

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The Year Book of Cardiology for 19 6 contains abstracts of selected reports in cardiology for the convenience of the busy physician Even though the reports are highly selected by the editors and their respective assistants the reader has an opportunity to review rapidly some of the studies published in cardiology in recent months. The abstracts are not critically reviewed by the contributors. They reflect the findings and opinions of the authors of the original publications. The comments of the contributors of each abstract are extremely valuable and should be appreciated by readers who failed to study the original publications closely This is a very good *Year Book* and all cardiologists will find owning and reading it extremely profitable

An Atlas of Non invasive Techniques By Aldo A Luisada M.D Gloria L. Perez M D and Pachal a K Bhat M D Springfield, Ill., 19 6 Charles C Thomas, Publisher 5o8 pages. Price $34 50

This atlas consists of 2o1 illustrations of non invasive recordings of cardiac hemodynamic phenomena with a fairly detailed legend of interpretations. The recordings are excel lent and the interpretations are clear The simultaneous recordings include tracings of common problems in cardiology such as heart sounds carotid artery pulsations, electrocar diograms, jugular vein pulsations echocardiograms cardiac apex pulsations, and others. The atlas is a good one which should assist residents and fellows training in cardiology in learning the interpretation and application of these tracings. Beginners will find it profitable to own this atlas and learn how these tracings reflect normal and abnormal cardiac disease states. This is a good addition to the literature in cardiology

CRC Immune RNA. Edited by E P Cohen Cleveland 19 6 CRC Press, Inc., 114 pages. Price $2?.?0

The book edited by Cohen consists of little more than 100 pages which succinctly summarize the role of RNA in immu nology The advances in immunology in recent years have been explosive by comparison with the distant past With the interest in immunological problems in medicine and cardio vascular diseases a better knowledge of the role of RNA complexes in this aspect of molecular biology should assist all physicians including cardiologists in understanding many diseases they treat The five papers which constitute this publication summarize very well the problems related to RNA immunology The interest in organ transplantation and immunosuppressant therapy renders it mandatory that physi cians learn and know the language and the fundamental concepts of immunology This includes the role of RNA and its various components and complexes in diseases states. This is a very good book and worth owning for reference

Introduction to Echocardiography By Ian G McDonald Springfield Ill 1976 Charles C Thomas Publishers, 2?0 pages. Price $?2.50

McDonald has added another good book to the many appearing recently on echocardiography The book is intended for beginners It is well written and includes a brief introduc tion to the physics of sound the principles of the recorder and recording as well as the role of echocardiography in clinical practice The illustrations are good and the bibliography is grouped in accordance with the disease and anatomic struc ture under study This is quite convenient for the reader It will help all physicians who interpret and record echocardio grams. This is one of the best books available today on the subject for beginners. It is highly recommended.

Books received

Directory of On going Research in Smoking and Health Government Printing Office National Clearinghouse for Smoking and Health Atlanta Ga 1976 Bureau of Health Education 397 pp Price $4 60

Pocket Consult Diuretics Edited by Mary Jo Reilly Washington D C 1976 American Society of Hospital Pharmacists 121 pp Price $5 00

Techniques in Bedside Hemodynamic Monitoring By John Speer Schroeder and Elaine Kiess Daily St Louis 1976 The C V Mosby Company 203 pp Price $7 25

Hypertension A Policy Perspective By Milton C Weinstein and William B Stason Cambridge Mass 1976 Harvard University Press 243 pp Price $15 00

Advances in the Management of Clinical Heart Disease vol 1 Edited by Charles P Bailey M D Mount Kisco N Y 1976 Futura Publishing Company 427 pp Price $34 95

Stroke Edited by F J Gillingham C Mawdsley and A E Williams New York 1977 Churchill Livingstone 535 pp Price $27.50

Legislative Action to Combat Smoking Around the World World Health Organization Geneva 1976 Health & Biomedical Information Program WHO 28 pp Price $2 40

Stroke A Doctor s Personal Story of His Recovery By Charles Clay Dahlberg M D and Joseph Jaffe M D New York 1977 W W Norton & Company Inc 200 pp Price $8 95

Controlling the Spread of Infection 2nd ed By Betty McInnes R N B Sc N M Sc St Louis 1977 The C V Mosby Company 107 pp Price $5 95

Adult and Child Care A Client Approach to Nursing By Janet Miller Barber R N Lillian Gatlin Stokes R N and Diane McGovern Billings R N St Louis 1977 The C V Mosby Company 948 pp Price $17 95

Announcements

British Cardiac Society meeting

The autumn meeting of the British Cardiac Society will be held on November 24 and 25 1977 at the Imperial College of Science and Technology in London It will be a joint meeting with the Swedish Society of Cardiology A limited number of reservations are still available for physicians and surgeons in the fields of cardiology cardiac surgery and pediatric cardiology who are not members of the Society The registration fee of £ 25 00 (approximately $43 U S) should be sent immediately to The Honorary Secretary British Cardiac Society 2 Beaumont Street London W1 England

1978 AMSA UTMB National Student Research Forum

The 1978 AMSA UTMB National Student Research Forum sponsored by the American Medical Association and The University of Texas Medical Branch will be held in Galveston on April 26 through 29 1978 The forum is open to medical students graduate students associated with medical schools and interns and residents who will compete in one of these categories based on their classification at the time of participation Research in both clinical and basic sciences will be included

Participants are selected solely on the basis of an abstract of the presentation which must be submitted with the formal application before February 2 1978 Participants in competition for the Excellence of Research Awards will be required to submit a formal manuscript Monetary and plaque awards will be given in the following categories liver disease demyelinating diseases cardiovascular research immunology and infectious diseases neuroscience pharmacology and surgery

For further information and application forms contact AMSA UTMB National Student Research Forum Room 209 Basic Sciences Building The University of Texas Medical Branch Galveston TX 77550

American Heart Journal

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Editorial

Prevalence of primary and secondary hypertension

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It is well established that the risk of cerebrovascular and cardiovascular complications increases gradually with increasing blood pressure. It is also documented that there is a high prevalence of blood pressure increase to that level which clearly warrants treatment. Thus, 10 to 15 per cent of middle aged men and women in various countries seem to benefit from treatment.

The proportion of the total hypertensive population with demonstrable causes of the hypertension is, however, not definitely known. In various textbooks and reviews the prevalence of secondary hypertension has been estimated to be 10 to 20 per cent. These figures have usually been based on studies in series of hospitalized patients, but there are several reasons to suspect that the prevalence of secondary hypertension is overestimated in these selected groups of patients. It is important to establish the prevalence of secondary hypertension since the investigations that are currently undertaken before treatment are largely aimed at detecting secondary forms of hypertension in which the patients might be cured by specific treatment such as surgery. The diagnostic investigations are also aimed at detecting hypertensive heart complications and renal complications, as these findings have been shown to carry a poorer prognosis,[1] calling for a closer supervision and more intensive treatment.

The prevalence of secondary hypertension is certainly not the same in all countries of the world because of varying prevalence of the conditions leading to, for example, renal parenchymal damage such as glomerulonephritis and pyelonephritis. A decreasing incidence of some of these conditions, such as analgesic nephropathy, is also to be expected.

Several investigators have shown that a large part of the hypertensive individuals in different populations are unknown, and any measure aiming at detecting and treating the major part of the hypertensive individuals in a population would increase the cost of the medical services. In this situation it is important to acquire information concerning the extent of examinations needed. A high prevalence of secondary, presumably curable hypertension would warrant more extensive preliminary investigations as would a high frequency of patients with hypertensive organ damage.

In a recent investigation we have been able to estimate the prevalence of primary and secondary hypertension in middle aged men in Sweden. Many of the economic and social circumstances as well as the disease panorama of this population is similar to that of several other countries. Thus it is probable that these findings can be extrapolated to these other populations.

The study population consisted of a randomly selected third of all men aged 47 to 54 years and

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Table I The prevalence of primary and secondary hypertension (n = 686) The number of previously known cases are given with brackets

	No	%
Renoparenchymal disease	25	3 6
Chronic glomerulonephritis	15 (15)	
Gouty nephropathy	3 (1)	
Renal tuberculosis	4 (4)	
Analgesic nephropathy	*1 (1)*	
Renal dysplasia	2 (1)	
Renovascular disease	4 (1)	0 6
Aortic coarctation	1 (1)	0 1
Primary aldosteronism	1 (1)	0 1
Primary hyperparathyroidism	2 (1)	0 3
Suspected but not proved unilateral hydronephrosis	7 (2)	1 0
Primary hypertension	646	94 2

who were residents of Goteborg, Sweden These men belonged to the intervention group of a multifactor primary preventive trial[6] Of those 9,996 men who were invited to the screening examination 7,455 (75 per cent) attended It has been shown that the non participants differed from the participants with respect to mortality and several social variables, but there were no indications that diseases leading to secondary hypertension were more common among the non participants[7]

In the first run those who were not receiving antihypertensive treatment and whose blood pressures were above 175 mm Hg systolic blood pressure (SBP) or 115 mm Hg diastolic blood pressure (DBP) were recalled within 2 weeks to have their blood pressures remeasured Those who still had blood pressures above these limits and all those who were on antihypertensive treatment were examined for secondary hypertension The screening methods and the investigations at the Hypertension Clinic have been reported in detail elsewhere[4, 6]

The examinations of the hypertensive patients consisted of a careful clinical scrutinizing for possible secondary hypertension The more complicated methods were performed in certain age groups--random samples of the total hypertensive group The investigations included a complete physical examination with auscultation of the heart and lungs, palpation of the femoral arteries and peripheral pulses, examination of the occular fundi, and a battery of laboratory tests including measurement of serum electrolytes and creatinine urine test for albuminuria and urinary sediment urine culture, and determination of renal concentration capacity with a 13 hour thirst test and, if the latter result was abnormal a vasopressin tannate test Isotope renography was carried out in the 287 men born in 1915, 1916 1920, and 1921 using a standard method and apparatus Intravenous pyelography (in 52 men) and renal aortography (in 12 men) were also performed with standard methods according to special indications Catecholamine concentrations were determined in all 58 men born in 1921 using a method described by von Euler and Floding[8] On the basis of the results of these investigations and a thorough examination of each patient s case records, a diagnosis was recorded using the criteria given below

Renoparenchymal disease

1 The diagnosis of chronic glomerulonephritis required persistent or intermittent albuminuria or hematuria or both, without there being another cause of these abnormalities

2 Renal tuberculosis was recorded when there was a history of pulmonary or renal tuberculosis, or both, with tubercle bacilli in the urine

3 Gouty nephropathy was recorded in the presence of known arthritis urica and lowered concentration ability (vasopressin tannate test < 800 mmol /Kg H_2O)

4 Renal dysplasia was defined as one small kidney without a history of urinary tract infections A kidney was considered small if it was over 2 cm shorter than the other kidney and less than 10 cm in length with oddly shaped or club like calices on the intravenous pyelogram[11]

5 Phenacetin nephropathy was recorded in patients with a long standing history of abuse lowered urinary concentration ability and signs of papillary necrosis on the intravenous pyelogram

6 Chronic pyelonephritis required a history of recurrent urinary tract infections and a lowered urinary concentration ability

Renovascular disease

Screening for renovascular disease was carried out by isotope renography Patients with abnormal renograms were admitted to hospital for renal aortography and other investigations Arteriographic verfication was required for a

diagnosis of renal artery stenosis or intrarenal occlusion. Abnormally high ipsilateral renin secretion or normalization of the blood pressure after surgery was not required for this diagnosis. Isotope renography was also performed if there were clinical signs of renovascular disease—for example, abdominal murmurs, drug resistant or accelerating hypertension, or increasing serum creatinine levels.

Primary aldosteronism

A hospital-verified diagnosis was required. Patients with spontaneous hypokalemia or hypokalemia during diuretic treatment whose serum potassium levels did not become normal after stopping treatment were admitted to hospital for investigation.

Primary hyperparathyroidism

A hospital-verified diagnosis was required. Serum calcium and phosphorous were not routinely screened.

Pheochromocytoma

A hospital-verified diagnosis was needed. Catecholamines in urine were determined only in men born in 1921.

Of the 7,455 men who were screened, 686 (9 per cent) had hypertension according to the above-mentioned criteria. Of these, 60 per cent were untreated, 23 per cent were treated but had blood pressure at screening above SBP 175 or DBP 115 mm Hg, and only 17 per cent had an acceptable control of their blood pressure. The number and percentage of cases with various types of hypertension appears in Table I. In seven cases of hydronephrosis (two previously known and five newly detected) we could not determine whether or not the hypertension was caused by the hydronephrosis and the resulting partial obstruction to urinary flow. Three patients did not become normotensive after operation and needed continuing antihypertensive treatment, and four patients were not operated on because they became normotensive on drug treatment and there were no other indications for operation.

Thus, a specific cause of hypertension was found or reasonably suspected in only 40 of the 686 patients (6 per cent). Eight patients had previously undergone surgical treatment. In only two cases did the patients' investigation lead to surgical intervention, and both these patients required antihypertensive treatment one year after their operations but lower doses were needed than before.

The methods of recognizing secondary hypertension were those normally used in clinical practice. Owing to the limited capacity of the laboratory, an isotope renogram was carried out only in four randomly selected age groups. In patients with hypertension refractory to treatment, investigation for renovascular causes was also carried out in the other age groups. Thus, most cases of renovascular hypertension amenable to surgical treatment were probably detected. Parenchymatous kidney disease without abnormal laboratory findings and with normal serum creatinine levels and concentration capacity may have been present without being detected. However, these patients had probably minor kidney damage, which in most cases would not have been treated other than with hypotensive drugs even if discovered. Primary aldosteronism was probably excluded with a relatively high degree of certainty. Primary hyperparathyroidism as a cause of hypertension may also have been present in more than the two cases who were found in our series since serum calcium was not measured routinely.

Thus, the prevalence of secondary hypertension was lower in this study than according to other estimates.[1-3] Our analysis is, however, the first one which has been performed in subjects derived from screening of a general population sample. Furthermore, we only studied men aged 47 to 54 years. The prevalence of secondary hypertension might be higher in women or in younger men. Our results suggest, however, that the risk of missing cases of secondary hypertension in middle-aged men is small and extensive investigations do not seem to be necessary in hypertensive subjects found at screening. In patients with hypertension referred to hospital, secondary hypertension is probably over-represented and more extensive routine investigations might be justified.

Isotope renography as a screening instrument for renovascular hypertension cannot be recommended. The prevalence of renovascular hypertension was low, and there were many false-positive renograms.[4] Thus, our results support the bad cost-benefit ratio found in recent analyses of urography and isotope renography as screening instruments for renovascular hyperten-

sion [15] and of comparisons of surgical and medical treatment of renovascular hypertension [16] Thus, the present data indicate that the resources for management of hypertension should be devoted more to case finding and treatment than to elaborate investigative measures

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Correlations between electrocardiographic, vectorcardiographic, and echocardiographic findings in patients with left ventricular overload

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Since Cabrera and Monroy first described systolic and diastolic overloading of the heart in 1952, considerable interest has been evoked in the subject. Most of these investigations, however, were rather qualitative, such as a comparison of vectorcardiographic pattern in patients with aortic stenosis and aortic regurgitation or patent ductus arteriosus. From the clinical point of view, it seems to be important to differentiate not only the type of overloading of the heart but also the severity of the disease. Yano and Pipberger have shown that radiographic heart size in patients with left ventricular overload correlated with (1) spatial magnitude of QRS, (2) Rx + Rz, (3) rightward displacement of J point, and (4) Rx peak time.

Recent advances in echocardiography have enabled noninvasive estimation of the wall thickness and cavity size of the left ventricle during life. Therefore, a left ventricular echogram was employed in this study to assess the morphological features of left ventricular hypertrophy with or without dilatation and to investigate electrocardiographic and vectorcardiographic findings quantitatively.

Methods and materials

A three-dimensional vectorcardiogram was recorded with a Fukuda Denshi Vectorcardiograph (VA-3C) instrument using the Frank lead system. Simultaneous recordings of the scalar leads X, Y, and Z were also taken at a speed of 100 mm./sec. The polarity in the three scalar leads was used as described by Frank, namely, positive deflections in scalar leads X, Y, and Z indicated leftward, inferior, and posterior direction, respectively. Maximum magnitude of the spatial QRS vector, QRS interval, and spatial QRS-T angle were calculated from the scalar lead. Rx peak time, Ry peak time, and Rz peak time were measured as the time interval between the onset of QRS and the peak of the R wave in the scalar leads X, Y, and Z.

A conventional electrocardiogram was also taken and the summed voltage of the S wave in V_1 and the maximum voltage of the R wave in Leads V_5 or V_6 ($SV_1 + RV_5$ or V_6) was measured as an index of left ventricular hypertrophy.

An echocardiogram was recorded with a Smith Kline Ekoline 20 ultrasonoscope, using a 2.25 MHz, 0.5 inch diameter transducer with a repetition rate of 1,000 impulses per second. The recording technique of the left ventricular echogram was as described by Popp and colleagues. Most patients were examined in the left decubitus position to provide clear visualization of the interventricular septum. Echoes from the anterior and posterior surfaces of the interventricular septum were identified as almost parallel and continual lines throughout an entire cardiac cycle.

The left ventricular minor diameter at end-diastole (LV diastolic diameter) was measured at the peak of the R wave of the simultaneously recorded electrocardiogram. Thickness of the posterior left ventricular wall was measured as

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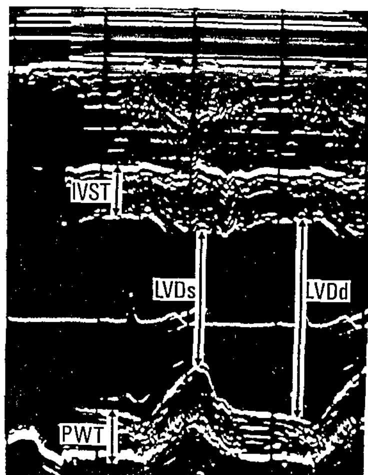


Fig 1 Echocardiographic recording of left ventricular diameter and wall thickness The damping control is abruptly reduced during the recording to delineate the pericardial and endocardial echoes *LVDd* = left ventricular diameter at end diastole *LVDs* = left ventricular diameter at end systole *IVST* = thickness of the interventricular septum *PWT* = thickness of the posterior left ventricular wall

described by Feigenbaum and associates [13] where the damping control was abruptly changed to record echoes from the endocardium and pericardium simultaneously on the same recording The distance between echoes from the anterior and posterior surfaces of the interventricular septum was assumed to represent its thickness Both measurements were made just before atrial systole (Fig 1) Left ventricular wall thickness (LV wall thickness) was calculated as the sum of the thickness of the ventricular septum and posterior wall

The study group consisted of 97 patients who ranged in age from 21 to 76 years (mean 48 4 years) and patients less than 20 years were excluded from this study All subjects presented echocardiographic evidence of left ventricular enlargement (LV wall thickness $\geqq$ 2 4 cm and/or LV diastolic diameter $\geqq$ 5 5 cm) The following subjects were not included in this study (1) patients with clinical evidence of myocardial infarction (2) patients with congenital heart disease who have the possibility of concomitant right ventricular overload such as ventricular septal defect and patent ductus arteriosus (3) patients with second or third degree A V block or patients with vectorcardiographic evidence of *intraventricular conduction disturbance,* (4) patients with extreme tachycardia (> 100 beats/min) or bradycardia (< 50 beats/min) and (5) patients with echocardiographic evidence of asymmetric septal hypertrophy (a ratio of the thickness of the ventricular septum to posterior wall $\geqq$ 1 3) or mitral stenosis (early diastolic slope of the anterior mitral valve $\leqq$ 30 mm / sec)

Table I Clinical diagnosis for 4 groups of the patients studied

Diagnosis	*Number of cases*		*Sex*		*Mean age (yr)*
			Male	*Female*	
Left ventricular hypertrophy (LVH)	40		32	8	55 [illegible]
Hypertensive heart disease		32			
Aortic stenosis		2			
Ischemic heart disease		4			
Others		2			
Left ventricular dilatation (LVD) without regurgitation	26		19	7	54 4
Hypertensive heart disease		14			
Congestive cardiomyopathy		8			
Others		4			
Aortic regurgitation (AR)	17		11	6	35 7
Mitral regurgitation (MR)	14		7	7	3[illegible] 9

According to their echocardiographic and hemodynamic findings the subjects were classified into four groups The clinical diagnosis sex and mean age for each group are presented in Table I The left ventricular hypertrophy (LVH) group consisted of 40 patients with LV wall thickness $\geqq$ 2 4 cm and LV diastolic diameter < 5 5 cm Most cases in this group were diagnosed to have systolic overload to the left ventricle systemic hypertension or aortic stenosis Patients with the dilated left ventricular cavity (LV diastolic diameter $\geqq$ 5 5 cm) were further divided into 3 groups 17 patients with pure or predominant aortic regurgitation (AR) 14 patients with

pure or predominant mitral regurgitation (MR) and 26 patients with left ventricular dilatation who were not associated with significant regurgitation (LVD). LV wall thickness was variable in these groups. Over half of the patients with LVD exhibited systolic overloading hemodynamically, i.e., systolic hypertension. Diagnostic angiocardiograms were performed in 13 patients with AR and 10 patients with MR. Aortic regurgitation was assessed to be 3+ in 9 patients and 4+ in 4 patients based on the criteria of Cohn and colleagues. Mitral regurgitation was 2+ in 1 patient, 3+ in 3 patients and 4+ in 6 patients according to the grading of Sellers and associates.[1]

Results

Table II presents echocardiographic, electrocardiographic and vectorcardiographic findings of the four groups. Correlation coefficients between electrocardiographic, vectorcardiographic and echocardiographic values are listed in Table III.

Heart rate did not differ significantly among the four groups. Figs. 2 and 3 show the relationship between left ventricular wall thickness and QRS magnitude in vectorcardiogram and electrocardiogram. A significant correlation was demonstrated between LV wall thickness and spatial maximum QRS magnitude in LVH ($r = 0.67$ and $p < 0.001$). A higher correlation was observed in LVH between LV wall thickness and $SV_1 + RV_5$ or V_6 ($r = 0.85$ and $p < 0.001$). In LVD, AR and MR, high QRS amplitude was observed not infrequently in cases without thickened left ventricular wall. Of 42 cases with LV wall thickness under 2.4 cm in these 3 groups, 38 cases (90 per cent) showed increased spatial maximum QRS magnitude of 2.0 mV or more and 39 cases (93 per cent) showed increased $SV_1 + RV_5$ or V_6 of 3.5 mV or more. However, modest correlations were observed in LVD between LV wall thickness and spatial maximum QRS magnitude ($r = 0.44$ and $p < 0.05$) and $SV_1 + RV_5$ or V_6 ($r = 0.43$ and $p < 0.05$).

On the other hand, LV diastolic diameter correlated significantly with spatial maximum QRS magnitude ($r = 0.74$ and $p < 0.005$) and $SV_1 + RV_5$ or V_6 ($r = 0.72$ and $p < 0.005$) in MR in whom LV wall thickness appeared nearly normal. These correlations were not significant in LVH, LVD and AR (Figs. 4 and 5).

Table II. Echocardiographic, electrocardiographic and vectorcardiographic findings in four groups

	LVH	LVD	AR	MR
Number of cases	40	[illegible]	1[illegible]	14
Heart rate	60 ± 19	69 ± 17	70 ± 14	70 ± 11
LVDd (cm)	4.5 ± 0.5	6.4 ± 0.6	6.6 ± 0.9	5.9 ± 1.0
LVWT (cm)	3.0 ± 0.4	2.1 ± 0.4	2.4 ± 0.3	2.0 ± 0.2
Spatial maximum QRS magnitude (mV)	2.51 ± 0.86	3.15 ± 1.17	3.[illegible] ± 1.1[illegible]	3.01 ± 1.1
$SV_1 + RV_5$ or V_6 (mV)	4.9 ± 1.6	5.5 ± 1.9	[illegible]	5.3 ± 1.4
QRS interval (msec)	88 ± 11	97 ± 10	97 ± 14	90 ± 11
Rx peak time (msec)	41 ± 9	54 ± 11†	58 ± 11†	45 ± 10
Ry peak time (msec)	48 ± 7	48 ± 7	[illegible] ± 9	49 ± 8
Rz peak time (msec)	[illegible] ± 6	54 ± 6	58 ± 9	[illegible]
Spatial QRS-T angle (degrees)	106 ± 46	141 ± 4	101 ± 53	[illegible] ± 43

*Statistically significant difference compared with LVH.
†Statistically significant difference compared with LVH and MR.
Values are means ± S.D.
‡Abbreviations: LVH = left ventricular hypertrophy; LVD = left ventricular dilatation; AR = aortic regurgitation; MR = mitral regurgitation; LVDd = left ventricular diameter at end-diastole; LVWT = left ventricular wall thickness.

Mean QRS interval was 88 ± 11 msec in LVH, 97 ± 10 msec in LVD, 97 ± 14 msec in AR and 90 ± 11 msec in MR and it was significantly greater in LVD and AR as compared with that in LVH ($p < 0.005$ and $p < 0.05$). Furthermore, QRS interval correlated significantly with LV diastolic diameter in LVD ($r = 0.64$ and $p < 0.001$), AR ($r = 0.77$ and $p < 0.001$) and MR ($r = 0.62$ and $p < 0.02$) as shown in Fig. 6. This correlation was not observed in LVH. A correlation between QRS interval and LV wall thickness was not significant in all groups.

Rx peak time, Ry peak time and Rz peak time were then compared with LV diastolic diameter (Fig. 7). Rx peak time showed significant correlation with LV diastolic diameter in LVD ($r = 0.72$ and $p < 0.001$) and in AR ($r = 0.71$ and $p < 0.005$). Ry peak time correlated well with LV diastolic diameter in MR ($r = 0.78$ and $p < 0.005$) and in AR ($r = 0.69$ and $p < 0.005$). Modest correlation was also observed between Rz peak time and LV diastolic diameter in MR ($r = 0.57$

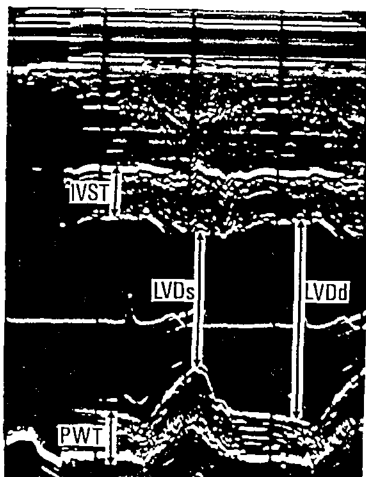


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According to their echocardiographic and hemodynamic findings the subjects were classified into four groups The clinical diagnosis sex and mean age for each group are presented in Table I The left ventricular hypertrophy (LVH) group consisted of 40 patients with LV wall thickness ≧ 2 4 cm and LV diastolic diameter < 5 5 cm Most cases in this group were diagnosed to have systolic overload to the left ventricle systemic hypertension or aortic stenosis Patients with the dilated left ventricular cavity (LV diastolic diameter ≧ 5 5 cm) were further divided into 3 groups 17 patients with pure or predominant aortic regurgitation (AR) 14 patients with

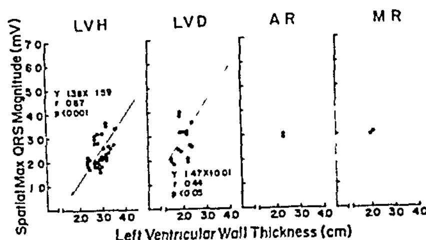


Fig 2 The relation between spatial maximum QRS magnitude (mV) and left ventricular wall thickness (cm) *LVH* = left ventricular hypertrophy *LVD* = left ventricular dilatation *AR* = aortic regurgitation *MR* = mitral regurgitation

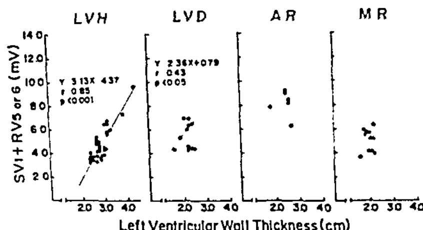


Fig 3 The relation between SV1 + RV5 or V6 (mV) and left ventricular wall thickness (cm) Abbreviations as in *Fig 2*

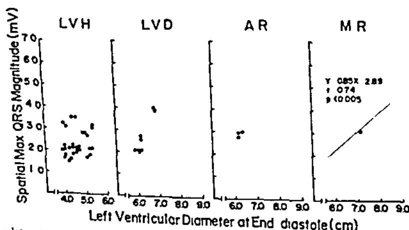


Fig 4 The relation between spatial maximum QRS magnitude (mV) and left ventricular diameter at end-diastole (cm) Abbreviations as in *Fig 2*

Table III Relationship between electrocardiographic, vectorcardiographic and echocardiographic findings in four groups

Y	Y	LVH		LVD		AR		MR	
		r*	p	r	p	r	p	r	p
LVWT	Spatial maximum QRS magnitude	0.67	<0.001	0.44	<0.05	0.45	NS	−0.27	NS
LVWT	SV + RV or V_6	0.85	<0.001	0.43	<0.05	0.41	NS	−0.36	NS
LVDd	Spatial maximum QRS magnitude	0.09	NS	0.18	NS	−0.13	NS	0.74	<0.005
LVDd	SV + RV or V_6	−0.12	NS	0.13	NS	0.18	NS	0.72	<0.005
LVWT	QRS interval	0.14	NS	−0.11	NS	−0.03	NS	−0.47	NS
LVDd	QRS interval	−0.01	NS	0.64	<0.001	0.77	<0.001	0.62	<0.0[illegible]
LVDd	Rx peak time	0.22	NS	0.72	<0.001	0.71	<0.005	0.29	NS
LVDd	Ry peak time	0.31	NS	0.33	NS	0.69	<0.005	0.78	<0.005
LVDd	Rz peak time	0.22	NS	−0.14	NS	0.36	NS	0.55	<0.05
LVWT	Spatial QRS-T angle	0.64	<0.001	0.19	NS	−0.06	NS	0.18	NS
LVDd	Spatial QRS-T angle	0.08	NS	0.25	NS	0.69	<0.005	−0.03	NS
QRS interval	Spatial QRS-T angle	0.06	NS	0.43	<0.05	0.74	<0.001	−0.16	NS

Abbreviations: r = correlation coefficient; p = probability by t test; LVH = left ventricular hypertrophy; LVD = left ventricular dilatation; AR = aortic regurgitation; MR = mitral regurgitation; LVWT = left ventricular wall thickness; LVDd = left ventricular diameter at end-diastole.

and $p < 0.05$). These observations indicated that dilatation of the left ventricle induces delayed inscription of the leftward directed force in LVD, left downward directed force in AR, and posterior downward directed force in MR.

Table IV presents the incidence of frontal and horizontal QRS configuration in the four groups. In order to study the effect of left ventricular dilatation on the configuration of the QRS loop, patients with LVD, AR, and MR were further divided into two subgroups: patients with LV diastolic diameter < 6.5 cm and LV diastolic diameter ≧ 6.5 cm. Horizontal QRS loop gave a counterclockwise configuration in most patients with LVH (90 per cent) and MR (86 per cent). In LVD and AR patients with larger LV diastolic diameter (≧ 6.5 cm.) showed increased incidence of figure of eight or clockwise configuration (75 per cent in LVD and 86 per cent in AR) in the horizontal plane. The frontal QRS loop gave a clockwise configuration in 73 per cent of LVH. No definite relation was observed between frontal QRS loop and LV diastolic diameter in LVD and AR. In MR, 10 of 14 cases inscribed clockwise in the frontal plane. The incidence of clockwise rotation increased in cases with larger LV diastolic diameter (89 per cent), although the difference was not statistically significant.

Spatial QRS-T angle correlated with LV wall thickness in LVH ($r = 0.64$ and $p < 0.001$) and with LV diastolic diameter in AR ($r = 0.69$ and $p < 0.005$). A significant correlation was also observed between spatial QRS-T angle and QRS interval in LVD ($r = 0.43$ and $p < 0.05$) and in AR ($r = 0.74$ and $p < 0.001$).

Discussion

Echocardiography is characterized by its ability to detect morphological and hemodynamic abnormalities of the heart noninvasively. Many investigators have demonstrated good correlations between echocardiographic and angiocardiographic measurements of left ventricular volumes and wall thickness.[16-2] Accordingly, the left ventricular echogram was employed in this study to investigate quantitatively electrocardiographic and vectorcardiographic findings of left ventricular hypertrophy with or without dilatation from morphological aspects.

Studies of normal adult populations[3, 4] have demonstrated that age trends are found in electrocardiographic and vectorcardiographic items. However, McCall and associates[5] and Blackburn and colleagues described only minor differences among the five decades over the age of 20 years. In the present study, regression analysis comparing age with QRS magnitude, QRS duration, R peak times and spatial QRS-T angle revealed no correlations in any of the four groups.

It has been appreciated for many years that a

Table IV Frontal and horizontal QRS configuration in four groups

	No of cases	*Frontal plane*			*Horizontal plane*		
		c†	8	cc	c	8	cc
LVH	40	29([illegible])	8(20%)	3(8%)	0(0%)	4(10%)	36([illegible])
LVD total	26	10(38%)	8(31%)	8(31%)	3(1[illegible])	9(3[illegible])	14([illegible])
LVDd < 6.5cm	14	[illegible](50%)	3(21%)	4([illegible])	0(0%)	3(21%)	11([illegible])
LVDd ≧ 6.5cm	12	3([illegible])	5(4[illegible])	4(33%)	3([illegible])	6(50%)	3([illegible])
AR total	17	6(3[illegible])	3(18%)	8(4[illegible])	2(1[illegible])	[illegible](41%)	8(4[illegible])
LVDd < 6.5cm	10	4(40%)	[illegible](20%)	4(40%)	0(0%)	3(30%)	[illegible]
LVDd ≧ 6.5cm	7	2(29%)	1(14%)	4([illegible])	[illegible]	4([illegible])	1(14%)
MR total	14	10([illegible])	3([illegible])	1([illegible])	0(0%)	2(14%)	12([illegible])
LVDd < 6.5cm	5	2(40%)	2(40%)	1([illegible])	0(0%)	1([illegible])	4([illegible])
LVDd ≧ 6.5cm	9	8(89%)	1(11%)	0(0%)	0(0%)	1(11%)	8([illegible])

*Statistically significant difference compared with LVDd < 6.5 cm.

†Abbreviations: c = clockwise rotation; 8 = figure of eight; cc = counterclockwise rotation; LVH = left ventricular hypertrophy; LVD = left ventricular dilatation; AR = aortic regurgitation; MR = mitral regurgitation; LVDd = left ventricular diameter at end diastole.

relationship exists between the muscle thickness or mass of the left ventricle and QRS magnitude. Bennett and Evans have recently reported the correlation between voltage measurements and left ventricular mass determined by echocardiography. The mechanisms by which anatomic ventricular hypertrophy or dilatation produces increased voltage are generally considered as follows: (1) decreased internal resistance of muscle fiber and increased current flow in conducting medium, (2) increased surface area and greater thickness of wall of hypertrophied ventricle, (3) closer proximity of heart to chest wall, (4) tangential spread of activation wave through wall of hypertrophied ventricle, and (5) Brody effect.

In the present study, good correlations were demonstrated in LVH between LV wall thickness and spatial maximum QRS magnitude or SV + RV or V. Consequently, LV wall thickness could be a major determinant of QRS magnitude in cases with left ventricular hypertrophy. In contrast, it was suggested that LV wall thickness itself was not a predominant cause of the increased QRS magnitude in LVD, AR, and MR, although modest correlations between LV wall thickness and QRS magnitude were observed in LVD. In these groups, the cavity size of the left ventricle was supposed to play a significant role in the augmented QRS magnitude. Especially in MR, significant correlations were obtained between LV diastolic diameter and spatial maximum QRS magnitude or $SV_1 + RV_5$ or V.

In this group, nearly normal and uniform LV wall thickness would be responsible for these correlations.

Prolongation of QRS interval or delayed ventricular activation time has long been considered to be one of the criteria to diagnose left ventricular hypertrophy. However, some authors described that actual delay of ventricular activation is surprisingly small and is not a constant feature in concentric left ventricular hypertrophy. In the present study, prolongation of QRS interval was also less evident in LVH and no correlation was demonstrated between LV wall thickness and QRS interval in this group. Therefore, prolonged QRS interval or delayed ventricular activation time, which is compatible with Rx peak time, could not be attributed to concentric left ventricular hypertrophy per se.

On the other hand, it was of interest that left ventricular dilatation was associated with prolonged QRS interval. A good correlation was observed between LV diastolic diameter and QRS interval in LVD, AR, and MR. Several authors reported that left ventricular dilatation might produce prolongation of QRS interval. Rosenbaum and colleagues reported that intraventricular conduction delay or block could be induced by ventricular dilatation. They attributed the incomplete right bundle branch block pattern in atrial septal defect and left anterior hemiblock in aortic regurgitation to an elongated conduction pathway due to ventricular dilatation. In addition, in extreme left ventricular

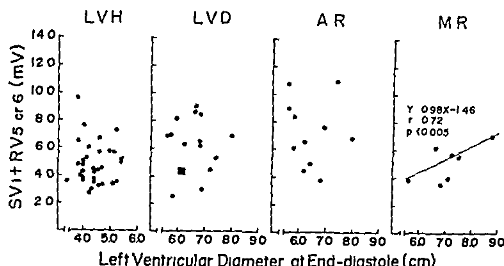


Fig 5 The relation between SV + RV or V (mV) and left ventricular diameter at end diastole (cm) Abbreviations as in *Fig 2*

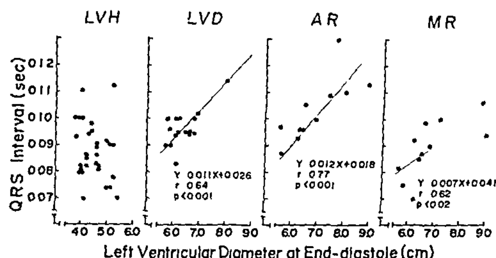


Fig 6 The relation between QRS interval (sec) and left ventricular diameter at end diastole (cm) Abbreviations as in *Fig 2*

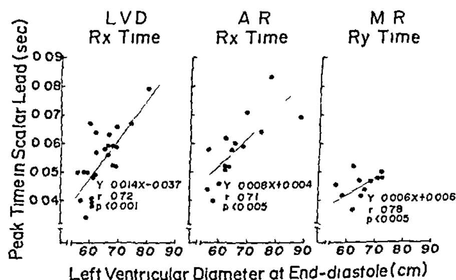


Fig 7 The relation between Rx peak time (sec) and left ventricular diameter at end diastole (cm) in left ventricular dilatation (*LVD*) and aortic regurgitation (*AR*) and between Ry peak time and left ventricular diameter at end diastole in mitral regurgitation (*MR*) Left ventricular diameter also correlated with Ry peak time in AR (r = *0 69* p < *0 005) and with Rz peak time in MR (r = 0 55 p < 0 05)*

Table IV Frontal and horizontal QRS configuration in four groups

	No of cases	Frontal plane			Horizontal plane		
		c†	8	cc	c	8	cc
LVH	40	29(73%)	8(20%)	3(8%)	0(0%)	4(10%)	36(90%)
LVD total	26	10(38%)	8(31%)	8(31%)	3(12%)	9(35%)	14(54%)
LVDd < 6.5cm	14	7(50%)	3(21%)	4(29%)	0(0%)	3(21%)	11(79%)
LVDd ≧ 6.5cm	12	3(25%)	5(42%)	4(33%)	3(25%)	6(50%)	3(25%)
AR total	17	6(35%)	3(18%)	8(47%)	2(12%)	7(41%)	8(47%)
LVDd < 6.5cm	10	4(40%)	2(20%)	4(40%)	0(0%)	3(30%)	7(70%)
LVDd ≧ 6.5cm		2(29%)	1(14%)	4(57%)	2(29%)	4(57%)	1(14%)
MR total	14	10(71%)	3(21%)	1(7%)	0(0%)	2(14%)	12(86%)
LVDd < 6.5cm	5	2(40%)	2(40%)	1(20%)	0(0%)	1(20%)	4(80%)
LVDd ≧ 6.5cm	9	8(89%)	1(11%)	0(0%)	0(0%)	1(11%)	8(89%)

Statistically significant difference compared with LVDd < 6.5 cm.

†Abbreviations c = clockwise rotation, 8 = figure of eight cc = counterclockwise rotation LVH = left ventricular hypertrophy LVD = left ventricular dilatation AR = aortic regurgitation MR = mitral regurgitation LVDd = left ventricular diameter at end-diastole

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In this group nearly normal and uniform LV wall thickness would be responsible for these correlations

Prolongation of QRS interval or delayed ventricular activation time has long been considered to be one of the criteria to diagnose left ventricular hypertrophy However some authors described that actual delay of ventricular activation is surprisingly small and is not a constant feature in concentric left ventricular hypertrophy In the present study prolongation of QRS interval was also less evident in LVH and no correlation was demonstrated between LV wall thickness and QRS interval in this group Therefore prolonged QRS interval or delayed ventricular activation time which is compatible with Rx peak time could not be attributed to concentric left ventricular hypertrophy per se

On the other hand it was of interest that left ventricular dilatation was associated with prolonged QRS interval A good correlation was observed between LV diastolic diameter and QRS interval in LVD AR and MR Several authors reported that left ventricular dilatation might produce prolongation of QRS interval Rosenbaum and colleagues reported that intraventricular conduction delay or block could be induced by ventricular dilatation They attributed the incomplete right bundle branch block pattern in atrial septal defect and left anterior hemiblock in aortic regurgitation to an elongated conduction pathway due to ventricular dilatation In addition in extreme left ventricular

dilatation, it is said that there is a decreased density of the junctions between Purkinje and ordinary muscle [41] This may be another possible cause of prolongation of QRS interval Our previous report[4] also suggested that prolongation of QRS interval could be induced by ventricular dilatation experimentally in aortic regurgitation The present result further confirmed these observations

In addition significant correlations were demonstrated between LV diastolic diameter and Rx peak time *in LVD, LV diastolic diameter and* Rx and Ry peak times in AR and LV diastolic diameter and Ry and Rz peak times in MR These observations indicated that dilatation of the left ventricle would cause conduction delay mainly to the left lateral wall in LVD, to the inferolateral wall in AR and to the inferoposterior wall in MR The exact mechanism of these differences is not clear To some extent, this would be related to the different configuration of the dilated left ventricle among the three groups Concomitant right ventricular hypertrophy should be also taken into consideration in MR

Horizontal QRS configuration was also affected by left ventricular dilatation Patients with larger LV diastolic diameter (≧ 6 5 cm) in LVD and AR more frequently inscribed in the figure of eight or clockwise direction Various configurations of the horizontal QRS loop have been described in left ventricular hypertrophy [3,10,13,17,43,47] However *their clinical significance* does not seem to be fully appreciated Hidaka[47] reported the increased incidence of figure of eight or clockwise horizontal QRS loop in aortic regurgitation as compared with hypertensive heart disease Yano and Pipberger[10] also reported that narrow or figure of eight configuration in the horizontal plane was frequently found in advanced left ventricular overload with roentgenographic cardiac enlargement and congestive heart failure They supposed that this horizontal QRS loop deformity was closely related to dilatation of the left ventricle Present results add further support to the concept that left ventricular dilatation is mainly responsible for the horizontal QRS loop deformity in LVD and AR

It has also been reported[10,43-46] that figure of eight or clockwise configuration of the horizontal QRS loop is associated with prolonged QRS interval or delay of Rx peak time In the present series delay of Rx peak time was suggested to be closely related to these QRS loop deformities With prolongation of Rx peak time it reaches or exceeds Rz peak time As a consequence, it seems likely that delay of Rx peak time could provide a narrow, figure of eight or clockwise configuration in the horizontal plane

Some authors[43,44] have ascribed these QRS loop deformities to incomplete left bundle branch block However in the present study, QRS interval and Rx peak time were observed to *increase gradually with LV diastolic diameter* concomitant with the QRS loop abnormality Moreover, Bell and associates[48] described the rapid reversibility of the abnormal QRS configuration after corrective aortic valve surgery We have also noted that the regression of Rx or Ry peak time and reversibility of the QRS loop deformities occur with reduction of LV diastolic diameter after successful treatment in LVD or corrective surgery in MR These observations seemed to support the concept that left ventricular dilatation can alone lead to a prolongation of QRS interval, delay of Rx peak time and horizontal QRS loop deformities in the absence of ventricular conduction defect of the bundle branch block type

Summary

Left ventricular echocardiography was employed to assess the vectorcardiographic and electrocardiographic *manifestations of left ventricular* hypertrophy with or without dilatation Based upon their echocardiographic and hemodynamic findings 97 subjects were divided into four groups, 40 patients with left ventricular hypertrophy (LVH) 26 patients with left ventricular dilatation (LVD) 17 patients with aortic regurgitation (AR) and 14 patients with mitral regurgitation (MR)

Left ventricular wall thickness the sum of the thickness of the ventricular septum and posterior wall, correlated well with spatial maximum QRS magnitude (r = 0 67) and $SV_1 + RV_5$ or V_6 (r = 0 85) in LVH On the other hand, dilatation of the left ventricle seemed to play an important role in the augmented QRS voltage in LVD AR, and MR

A significant correlation was observed between left ventricular diameter at end diastole (LV diastolic diameter) and QRS interval in LVD

AR and MR LV diastolic diameter also correlated with Rx peak time in LVD Rx and Ry peak times in AR and Ry and Rz peak times in MR In addition horizontal QRS configuration was affected by left ventricular dilatation In LVD and AR the incidence of a figure of 8 or clockwise configuration increased in cases with LV diastolic diameter ≥ 6 5 cm Thus, left ventricular dilatation was demonstrated to be responsible for prolongation of QRS interval In LVD and AR it could induce delay of Rx peak time and consequently QRS loop deformity in the horizontal plane

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Prognosis of infants with coarctation of aorta

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Infants with coarctation of the aorta and congestive heart failure in the first six months of life usually represent a mixed group both pathologically and clinically [1] The clinical course and prognosis of infants with coarctation of the aorta are reviewed in relation to their associated cardiac defects and their medical or surgical management

Material

Thirty six infants with coarctation of the aorta who developed congestive heart failure in the first six months of life were seen between 1960 and 1974 There were 24 males and 12 females Fourteen were seen within one month of age ten during the second month and twelve between the third and sixth month They were followed from 18 months to 15 years (mean 4 5 years) Ten of the twelve patients referred between the third and sixth month of life survived

Usually they had feeding problems poor weight gain dyspnea tachycardia cardiomegaly and hepatomegaly All infants had congestive heart failure All had absent or weak femoral artery pulsation and elevation of blood pressure in the upper extremity Of those who had measurement of blood pressure performed in the upper and lower extremity on the initial examination two had a systolic gradient of 20 mm Hg 16 had a systolic gradient of 20 to 50 mm Hg and ten had a systolic gradient of more than 50 mm Hg All had cardiomegaly on x ray examination Initial electrocardiogram showed 15 patients with combined ventricular hypertrophy 16 with right ventricular hypertrophy and five with left ventricular hypertrophy Twelve patients had right atrial hypertrophy and one patient had biatrial hypertrophy in addition to the ventricular hypertrophy

All of the infants were treated by vigorous medical management including correction of acidosis administration of digitalis and diuretics All but one patient had cardiac catheterization during the initial hospitalization When clinical improvement was not apparent and there was no evidence of central nervous system damage surgery was recommended The operative procedures included relief of coarctation ligation and division of a patent ductus arteriosus and banding of the pulmonary artery in the presence of a large ventricular septal defect

Hemodynamic studies

The patients were divided into four groups according to their findings at cardiac catheterization

Group I Twelve patients with isolated coarctation of the aorta The coarcted area was at the level distal to the left subclavian artery The pulmonary artery pressure varied from normal to systemic level In one it was 15/5 mm Hg in eight patients the systolic pulmonary artery pressure was 25 to 50 mm Hg and in two patients the systolic pulmonary artery pressure was more than 50 mm Hg One patient was not catheterized in infancy

Group II Five patients with coarctation of the aorta and a patent ductus arteriosus Three patients had coarctation at the preductal level and two had coarctation distal to the origin of the

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anatomical defects (Table II) Of the 12 Group I patients with isolated coarctation only one had surgery in infancy There were six patients in this group operated upon after infancy without surgical mortality One infant without surgery died at home probably due to aspiration of food Four patients are doing well and are awaiting coarctectomy

In five Group II patients who had coarctation and a patent ductus arteriosus three had coarctectomy and ligation of the patent ductus during infancy and all survived Of the two patients who were not operated upon one died and one is doing well

In nine Group III patients with coarctation and ventricular septal defect with or without a patent ductus arteriosus five patients were subjected to coarctectomy with a patent ductus arteriosus ligation and pulmonary artery banding in infancy One of these died two months postoperatively and two patients died several years later One died at 7 years 9 months of age two years after the closure of the ventricular septal defect and removal of the pulmonary artery band One died at 3 years 3 months after probable subacute bacterial endocarditis and lung abscess One patient who had coarctectomy at age 2 years is doing well with a small ventricular septal defect Of the two surviving patients who had coarctectomy and pulmonary artery banding one is doing well with an apparently non functioning pulmonary artery band and a small or spontaneously closed ventricular septal defect not visualized by cineangiogram The other lost to follow up had a persistent coarctation with a 80 mm Hg systolic gradient by blood pressure measurement and ventricular septal defect One baby with severe cerebral hypoxia died without surgery Two patients one age two years the other age three years have had no surgery yet and are doing well The ventricular septal defect appears to be getting smaller

In Group IV patients three babies died without surgery in infancy and seven underwent surgery with three deaths Four surviving patients are two children with transposition of the great vessels one child with post aortic valvulotomy and mitral valve replacement and one child with two coarcted areas who had coarctectomy and a patch graft The patients with transpositions are awaiting further surgery and the one with the double coarctation is surviving with a residual systolic gradient of 25 mm Hg The patient who had aortic valvulotomy and mitral valve replacement with a Bjork Shiley valve is doing extremely well two years after surgery

The over all surgical mortality rate was 26 per cent (6/23) The surgical mortality rate for those of less than one year of age was 37 5 per cent (6/16) There was no mortality when surgery was done after one year of age (0/7) In contrast there were 46 per cent (6/13) deaths in non-operated cases (Table II) Obviously there was a higher mortality rate in the groups of complicated coarctation of the aorta

Blood pressure in survivors

There were 17 survivors after surgery and seven survivors without operation Among the 17 patients ten had coarctectomy at less than one year of age and seven were operated upon between 3 to 8 years of age There were five patients operated within one month of age one each at 2 months and at 3 months two at 5 months and one at 8 months. Two of these ten operated in infancy have hypertension in the arms with a systolic gradient of more than 20 mm Hg between the blood pressures in the arms and that in the legs

There was no gradient of more than 10 mm Hg between the systolic arm blood pressures and leg blood pressures in patients operated upon after infancy However one patient who was operated at age 3 5 years and is now 16 years of age has mild hypertension of 140/60 mm Hg to 160/80 mm Hg This patient has a very mild residual coarctation on aortogram with a mean gradient of 15 mm Hg across the coarctation

Extracardiac anomalies

One patient with isolated coarctation developed subarachnoid hemorrhage at age 8 years due to a ruptured aneurysm of the anterior communicating artery After a bi frontal craniotomy with clipping of the aneurysm she subsequently underwent coarctectomy with success One patient with isolated coarctation also has agenesis of the right kidney

Autopsy findings

There were ten postmortem examinations among the 12 deaths five each with and without surgery Of the two late operative deaths who had what appeared to be functioning pulmonary

Table I Clinical data in patients with coarctation of aorta and VSD

Case	*Age at catheterization*	*PA pressure (mm Hg)*	*PDA*	*Surgery*	*Outcome*
2	2 mos	54/16	No	Coarctectomy at 2 yrs	Living and well VSD is small
8	1 mo	105/40	No	Coarctectomy and PA band at 2 mos	Died at 4 mos no autopsy
11	2 mos	110/45	Yes	Coarctectomy PDA division PA band at 13 mos VSD closure and removal of PA band at 5 yrs	Died at 7 9/12 yrs pulmonary hypertension on autopsy
12	2 mos	110/47	Yes	Coarctectomy PDA division PA band at 3 mos	Living and well VSD is small
19	6 mos	90/44	No	Coarctectomy PA band at 8 mos	Died at 3 3/12 yr small VSD pulmonary hypertension on autopsy
26	18 days	82/30	Yes	No	Died at age 5 mos VSD closed on autopsy
28	4 mos	90/35	No	Coarctectomy PA band at 5 mos	Moved persistent coarctation and VSD
31	1 mo	120/54	No	No	Living and well VSD is small
32	3 mos	95/30	No	No	Living and well with VSD and coarctation awaiting surgery

Table II *Mortality classified by associated cardiac defects and surgery or non surgery*

Group	*Catheterization findings*	*Number of cases*	*Deaths*			*Total deaths*
			Surgery in infancy	*Surgery after infancy*	*Non surgery*	
I	Isolated coarctation	12	0/1	0/6	1/5	1/12
II	Coarctation and PDA	5	0/3	0/0	1/2	1/5
III	Coarctation VSD with or without PDA	9	3/5	0/1	1/3	4/9
IV	Coarctation and complicated lesions	10	3/7	0/0	3/3	6/10
Total		36	6/16	0/7	6/13 (46%)	12/36 (33 3%)
			6/23 (26%)			

left subclavian artery Three had a pulmonary artery pressure of 80/35 40 mm Hg two 50/15 20 mm Hg

Group III Nine patients with coarctation of the aorta and ventricular septal defect with or without a patent ductus arteriosus All had elevated pulmonary artery pressure (Table I) The magnitude of the pulmonary blood flow was difficult to evaluate in this group of patients because of their unstable conditions some received oxygen during the catheterization However on cineangiographic examination all had large left to right shunt at the ventricular level

Group IV Ten patients with complex heart lesions in addition to the coarctation of the aorta There were three patients with transposition of the great vessels, two with atrioventricular canal two with hypoplastic aortic arch ventricular septal defect and patent ductus arteriosus one with supravalvular mitral stenosis one with severe aortic stenosis and mitral insufficiency and one had an atrial septal defect patent ductus arteriosus and two coarcted areas in the thoracic aorta

Clinical course surgical procedures and mortality

In general the coarcted segment was resected and anastomosis was achieved by running sutures at the posterior aspect and interrupted sutures at the anterior aspect or interrupted mattress sutures entirely Three patients received grafts at the coarctectomy site

The clinical courses varied according to the

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artery banding in infancy severe pulmonary hypertensive changes were found One had a *Heath Edwards Grade IV* hypertensive change *and the other Grade VI* hypertensive change One of these had cardiac catheterization at age 5 years and the right ventricular systolic pressure was *noted to be 100* mm Hg proximal pulmonary artery pressure was *80/40* mm Hg, and distal pulmonary artery 50/35 mm Hg He had surgical closure of the ventricular septal defect and debanding of the pulmonary artery at age 5 years However he developed murmur of a pulmonary insufficiency subsequently and had a repeat cardiac catheterization at age 6 5 years The pulmonary artery pressure was noted to be 110/ *50 mm* Hg and he died a year later suddenly The other patient came to the hospital at the age of 3 years with clinical findings compatible with sub acute bacterial endocarditis and on cardiac catheterization the proximal pulmonary artery pressure was 110/20 mm Hg and distal pressure was 85/55 mm Hg Of the three patients thought to have a large ventricular septal defect clinically, one had a completely closed ventricular septal defect and in the other two the ventricular septal defect was small on postmortem examination

Discussion

The mortality rate among patients with coarctation *of the aorta in the first year of life has been* variable [1-3] The surgical mortality rate of 33 to 41 per cent in earlier series[1-3] has decreased to 14 to 17 per cent in more recent reports [4-5] The present series has a surgical mortality rate of 26 per cent (6/23) and non surgical mortality rate of 46 per cent (6/13) It is difficult to compare the surgical mortality rates in each series since each report deals with different clinical and age groups The higher non surgical mortality rate in our series can be explained by the inclusion of patients with severe complicated cardiac lesions In general it seems apparent that surgery should be recommended in those patients who show no improvement with medical management There was virtually no mortality in the group with isolated coarctation and they had good response to medical management in infancy In the group with coarctation and ventricular septal defect coarctectomy and a pulmonary artery banding carried a high risk in our small series (3 out of 5) One died shortly after surgery and two died several years later It is discouraging that two of the three who survived *the initial surgery died* eventually with pulmonary hypertension despite functioning pulmonary artery band Perhaps primary closure of the ventricular septal defect under hypothermia in *addition to coarctectomy* in infancy is an alternative [6] It is of interest that in five of the nine Group III patients the ventricular septal defect had closed spontaneously or had become smaller This suggests that banding of the pulmonary artery at the time of coarctectomy may not be beneficial Persistent or residual coarctation with a systolic gradient of more than 20 mm Hg is not a common problem in our series even in patients operated upon in infancy (2 out of 10) We have seen no patients with recurrent coarctation, although it is known to occur [8] It is possible that the low recurrence is related to the surgical technique of using interrupted sutures as proposed by Mustard [9]

Several reports indicated a high incidence of hypertension and premature cardiovascular disease in patients operated for coarctation [1-11] Nanton and Olley[12] reported a 15 per cent incidence of unexplained hypertension in children operated between 1 year and 15 years Although we have observed only one patient with unexplained hypertension the incidence could possibly increase with prolonged follow up Our series is too small for meaningful comparison with others

It is now our feeling that coarctectomy is indicated if there is persistent congestive heart failure in infancy Infants with isolated coarctation or coarctation with patent ductus arteriosus have a good prognosis In infants with a large ventricular septal defect and coarctation three surgical approaches could be considered pulmonary artery banding and coarctectomy coarctectomy and primary closure of ventricular septal defect under hypothermia or coarctectomy alone with the hope that the ventricular septal defect will decrease in size with growth At the present time it appears that the approach will depend upon the preference and experience of the individual institution In infants with complicated cardiac lesions in addition to coarctation palliative or corrective surgery should be attempted

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minutes PPP for nucleotide assays was mixed with equal parts of ice-cool ethanol and frozen at −60°C until tested [5]

The concentrations of hemoglobin LDH and nucleotides were measured and the differences between test and control plasmas represented the amounts derived from blood cells by passage of EDTA blood through the columns The proportions of the total content that was liberated was calculated for each substance Since they were confined to the volume of plasma and EDTA solution after the liberation and not to the volume of blood a correction had to be made before comparison with the total blood content This was achieved by multiplying the increase in plasma concentrations with the factor 10/9 − Ht /100 where Ht represents the hematocrit

The EDTA added to blood before passage through the column could possible influence the degree of hemolysis produced To study this blood without addition of anticoagulants was forced through the column and mixed with EDTA solution immediately afterwards Native blood that had been passed through a tube without beads served as control PPP was prepared and the liberation of hemoglobin was determined A difference between the degree of hemolysis induced in native blood and in EDTA blood would reflect the effect of EDTA on the fragility of the red cell membranes

Assays Hemoglobin concentrations were determined by the method of Crosby and Furth [1] This method was fairly accurate for determination in plasma the coefficient of variation between duplicate samples being 5 0 The plasma heme levels were expressed in terms of oxyhemoglobin standards determined with the cyanmethemoglobin method [1] LDH measurements were done according to Wroblewski and LaDue at 25 C using commercial reagents

Microdetermination of ATP and ADP was done by the firefly luciferase method using a DuPont 760 Luminescence Biometer To make the method sufficiently sensitive 100 µl of ethanol EDTA extracts of PRP and standards were used instead of 20 µl With this modification a linear relationship between light emission and nucleotide concentrations in the actual range was obtained and it allowed determination of ADP levels lower than 0 05 µM The ADP was measured after conversion to ATP by a pyruvate kinase system [11] and the combined amounts of ATP and ADP were therefore determined in one plasma sample In another the conversion was not induced and ATP alone was measured ADP was then calculated as the difference between the two values Standard curves were made from ADP [*]

Platelet adhesiveness Native blood from the same subjects was collected in 5 ml plastic syringes and immediately used for platelet adhesiveness measurements by Hellem s modified method [2] Thus native blood was forced through the glass bead columns at the same speed that had been applied to the EDTA blood Platelets were counted in a hemocytometer according to Nygaard s method [2]

ADP in arterial plasma measurements and calculations To study whether trace amounts of ADP could be detected in arterial plasma blood was collected from the ascending aorta during catheterization in one and from puncture of the radial artery in three valve patients Arterial blood from four individuals who were catheterized because of coronary heart disease was used as control The blood was collected in EDTA solution PPP prepared and analyzed for hemoglobin LDH and adenine nucleotides

In order to evaluate the possible influence on platelet retention of ADP liberated intravascularly an estimate of the maximal concentrations of ADP that could theoretically be expected to occur as a hemolysis related phenomenon near the valve was made from the following data From the mean plasma LDH values and the blood volume the abnormal red cell breakdown could be calculated [3] Assuming that the cells were all destroyed by the prosthetic valve the intravascular breakdown per heart beat could be estimated Knowing the total ADP content and assuming further that the ADP was immediately diluted by the volume of a stroke output the maximal theoretical ADP levels near the valve could be calculated Since the elimination of ADP is very rapid [2] accumulation would not occur

Results

Whole blood contents The total contents of hemoglobin LDH ATP and ADP were quite similar in blood from patients with prosthetic aortic valves and healthy subjects (Table I) none

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Reduced platelet adhesiveness in patients with prosthetic ball valves Relation to adenosine diphosphate and mechanical trauma

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Patients with aortic ball valves have a disturbed platelet function[1] and their platelet adhesiveness, as measured in native blood with Hellem's modified method[2] is low[1] Hellem demonstrated that platelet retention in glass bead columns was dependent upon red cells or a substance present in red cells[3] later identified to be adenosine diphosphate (ADP)[4] Recently, it has been suggested that red cells are important because they alter flow patterns within the columns,[5] and that the ADP necessary for retention is derived from blood platelets[6, 7]

When platelets are exposed to ADP without stirring in vitro, further addition of ADP will induce a lower degree of platelet aggregation than without preincubation[8-11] the platelets have become refractory towards ADP[10] A reduced platelet adhesiveness was demonstrated in rabbits after intravenous infusion of ADP[12] and during intravascular hemolysis initiated by water installation[13] Disturbance of human blood in vitro or addition of ADP prior to testing reduced platelet retention in glass bead columns considerably[6] In patients with aortic ball valve prostheses some degree of continuous intravascular hemolysis is found[14] which might influence platelet behavior through a similar mechanism

This investigation was done in order to study whether the reduced adhesiveness in blood from ball valve patients could be due to ADP liberated intravascularly from red cells The total content of adenine nucleotides in blood from such patients was compared with that of normals The liberation of nucleotides during passage of blood through the glass bead columns was measured and a comparison made to the degree of hemolysis provoked Further, platelet adhesiveness was determined in the same individuals and related to the ADP liberated An attempt was made to detect circulating nucleotides in plasma from venous and arterial blood Finally, the theoretical trace concentrations of ADP that could occur near the prosthetic valves were calculated and the possible influence on platelet behavior was evaluated

Materials and methods

The study was done in eleven patients with single Starr Edwards aortic ball valves and eight healthy individuals Blood was carefully collected in plastic tubes containing ethylene diamine tetra acetate (EDTA) in order to achieve anticoagulation and avoid degradation of adenine nucleotides Nine parts of blood were mixed with one part of 0 077 M EDTA and is referred to as EDTA blood

Whole blood contents To determine the total blood content of hemoglobin, lactate dehydrogenase (LDH), adenosine triphosphate (ATP) and ADP 20 µl of EDTA blood was diluted to two ml in saline (pH 7 4) and frozen and thawed three times The concentrations measured were corrected for dilution with saline and EDTA solution

Effects of passage through glass bead columns EDTA blood was forced through glass bead columns at a speed of one ml per 9 2 seconds as described by Hellem,[2] in order to study the liberation of the various substances by this slight mechanical trauma EDTA blood that had been passed through a plastic tube at the same speed served as control Platelet poor plasma (PPP) was then prepared as follows The samples of EDTA blood were centrifuged at 1000 × g for 15 minutes the plasma carefully pipetted off and centrifuged in new tubes at 12000 × g for 15

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blood contained on average 138 μM of ADP and since the ADP liberated was supposed to be diluted by the 40 ml of plasma of a stroke output the maximal ADP concentrations derived from red cells would be in the range of 0 0012 μM Accumulation would not occur because ADP would rapidly be diluted and eliminated These calculations do not include ADP that might possibly appear from blood platelets by the release reaction

Discussion

The whole blood content of adenine nucleotides hemoglobin and LDH was not lower in patients with prosthetic ball valves than in healthy individuals in spite of increased red cell turnover as reflected by the elevated plasma LDH levels.[1] The total nucleotide content compares well with the results from other studies while a higher ATP ADP ratio has been reported[3] The bulk of adenine nucleotides in whole blood is located in the red cells and the platelets contribute only approximately 12 to 20 μM of ATP and 6 to 10 μM of ADP

The total concentrations of LDH in blood from ball valve patients compared well with the results from a previous study whereas somewhat higher normal levels then were found[1] The determination of the LDH content was however more accurate in the present investigation since the measurements were done in less diluted blood

The passage of EDTA blood through the glass bead columns exposed the red cells to a quite constant trauma since the variation in the degree of hemolysis induced was small Further the same degree of hemolysis was produced in both groups of subjects indicating that the stress inflicted by the ball valves had not weakened the red cell membranes Normal fragility of erythrocytes from ball valve patients has previously been revealed[2] as has a slightly higher liberation of LDH than of hemoglobin by mechanical trauma[5]

The increase in plasma concentrations of ATP and ADP after passage of EDTA blood through the column was most probably related to the hemolysis produced since the nucleotides and hemoglobin appeared in comparable proportions This is in accord with the results from a previous study from this institute in which a different method for hemoglobin determination was used[2] Zucker s group[4] found a similar liberation of ADP from heparinized blood but failed to reveal a corresponding increase in hemoglobin concentrations Less ADP was found to appear after passage of blood from subjects with low platelet retention[1] and it was suggested that the ADP was derived by release from platelets during the passage through the column[1] They stated however that the classic release reaction may not have been responsible since the liberation occurred at room temperature and was not prevented by acetylsalicylic acid or accompanied by measurable release of serotonin[1] Furthermore no indication of release has been revealed by electronmicroscopic studies of retained platelets[1] If release had occurred to any extent much higher ADP concentrations would appear as

Table III Liberation of hemoglobin lactate dehydrogenase adenosine triphosphate and adenosine diphosphate by passage of EDTA blood through glass bead columns in per cent of the whole blood content

Percent liberation of	Healthy individuals		Ball valve patients	
	Mean	S E M	Mean	S E M
Hb	0 0[illegible]	0 004	0 0[illegible]	0 00[illegible]
LDH	0 06[illegible]	0 011	0 0[illegible]	0 01[illegible]
ATP + ADP	0 0[illegible]8	0 010	0 0[illegible]1	0 0[illegible]
ATP	0 064	0 011	0 0[illegible]	0 00[illegible]
ADP	0 04[illegible]	0 011	0 04[illegible]	0 018

Table IV Retention of platelets by passage of native blood through glass bead columns total platelet counts hematocrit values and plasma LDH levels with level of significance on the differences between the values in 8 healthy subjects and 11 ball valve patients (N S = not significant) Liberation of hemoglobin in columns from native blood of 8 healthy subjects

	Healthy individuals		Ball valve patients		Level of significance
	Mean	S E M	Mean	S E M	
Platelet retention (per cent)	[illegible]1	2 3	34 2	5 0	p < 0 001
Platelets per μl	2[illegible]5 300	9 000	[illegible]	[illegible]	N S
Hematocrit (per cent)	45 6	1 [illegible]	4[illegible] 6	1 2	N S
Plasma LDH (U /L)	104 0	10 6	3[illegible]1 4	91 4	p < 0 01
Liberation of Hb (mg /100 ml)	9 3	1 0			

Table I The whole blood content of hemoglobin (Hb), lactate dehydrogenase (LDH), adenosine triphosphate (ATP), and adenosine diphosphate (ADP) Mean values and standard error of the mean in 8 healthy subjects and 11 patients with aortic ball valve prostheses

Total content of	*Healthy individuals*		*Ball valve patients*	
	Mean	*S E M*	*Mean*	*S E M*
Hb (G /100 ml)	12 64	0 51	12 74	0 42
LDH (U /L)	13 851	991	14 694	798
ATP + ADP (μM)	605 1	27 1	627 8	17 6
ATP (μM)	*453 1*	*30 2*	*474 6*	*15 7*
ADP (μM)	152 0	10 4	153 2	14 0

Table II Increase in plasma concentrations of hemoglobin lactate dehydrogenase adenosine triphosphate, and adenosine diphosphate by passage of EDTA-blood through glass bead columns A comparison between 8 healthy subjects and 11 patients with aortic ball valves

Liberation of	*Healthy individuals*		*Ball valve patients*	
	Mean	*S E M*	*Mean*	*S E M*
Hb (mg /100 ml)	10 1	0 7	9 4	0 6
LDH (U /L)	18 0	2 5	14 3	?9
ATP + ADP (μM)	0 54	0 08	0 55	0 05
ATP (μM)	*0 44*	*0 09*	*0 45*	*0 05*
ADP (μM)	0 10	0 02	0 10	0 04

of the differences were statistically significant The mean ATP ADP ratio was 3 6 and 3 2 in the two groups

Effects of passage through glass bead columns A slight increase in the plasma concentrations of hemoglobin, LDH and adenine nucleotides was found after passage of EDTA blood through the columns (Table II) and it was only possible to determine the ADP levels by increasing the sensitivity of the method as described The effect of the trauma was almost identical on blood from the two groups of subjects ATP and ADP appeared in proportions that did not differ significantly from those of whole blood

The amounts of hemoglobin, LDH and nucleotides liberated were calculated in per cent of the total content (Table III) None of the differences between the two groups were statistically significant The liberation of hemoglobin illustrated that passage through the columns represented only a minimal trauma to the blood cells since it corresponded to rupture of only one out of 2,000 erythrocytes Further a rather similar degree of hemolysis was produced in EDTA blood from the different individuals of both groups demonstrating that the effect of the trauma was quite constant Slightly more LDH than hemoglobin was liberated in the healthy individuals $p < 0.05$

The ATP and ADP appeared in proportions that did not differ from those of hemoglobin within each of the groups

The addition of EDTA to blood before expsoure to the glass beads did not affect the fragility of the red cell membranes since the liberation of hemoglobin from red cells of native blood by passage through the columns was similar to that of EDTA blood (Table IV), and the inter individual variation was equally small

Platelet adhesiveness The retention of platelets when native blood was forced through the columns was markedly lower than normal in the ball valve patients (Table IV), the reduction being highly significant ($p < 0.001$)

Intravascular hemolysis The elevation of the plasma LDH levels in the patients reflected a considerable degree of hemolysis

Adenine nucleotides in arterial plasma Low concentrations of hemoglobin and adenine nucleotides were measured in PPP from arterial and venous blood Thus the mean hemoglobin concentrations in arterial plasma from normals and valve patients were 5 2 and 6 8 mg /100 ml while the corresponding adenine nucleotide levels were 0 26 and 0 29 μM the mean ATP ADP ratio being 1 3 in each group In venous plasma, similar levels were found It is however unlikely that free nucleotides should be circulating in plasma as discussed below

The results of the calculations on hemolysis related liberation of ADP were A mean plasma LDH level of 381 U /L corresponds to a red cell half life of 20 days as compared to 27 5 days in normals [20] Considering the blood volume to be 5 3 L [2] the daily red cell breakdown would be equivalent to 96 ml of blood in the healthy subjects and to 132 ml in the ball valve patients Assuming that the cells of the extra 36 ml were destroyed by the prosthetic valve and that th heart rate was 70 cells of 0 36 μl of blood wer ruptured by each heart stroke Since the whol

normal platelet retention is mainly derived from red cells and not from platelets

The retention of platelets by passage of native blood through the columns was significantly reduced in the patients in spite of the normal liberation of ADP This low platelet adhesiveness could possibly be due to refractoriness towards ADP liberated from red cells during intravascular hemolysis The ADP concentrations that could be derived from red cells were however calculated to be far lower than the levels known to affect platelet behavior and ADP is rapidly eliminated from plasma It is concluded that the reduced platelet retention in blood from ball valve patients was most probably a result of trauma to the platelets inflicted by the valve and was not secondary to intravascular hemolysis

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found after addition of thrombin to platelet rich plasma [1]

In the present study the added EDTA would markedly inhibit platelet retention and release of ADP from platelets Moreover, the ATP ADP ratio was as high as in whole blood, which confirms that the nucleotides were derived mainly from red cells The hemolysis induced cannot be attributed to the addition of EDTA since plasma hemoglobin increased to the same extent when native blood was passed through the columns

Zucker s group [4] have demonstrated that the first step in platelet retention is adhesion of platelets to the glass beads, and that this reaction is independent of ADP Subsequent retention is caused by platelet-platelet interactions requiring ADP supposed to be derived from the reacting platelets This study demonstrates, however, that comparable amounts of ADP are liberated from red cells Lower ADP levels are able to induce platelet retention in platelet rich plasma and although red cells facilitate retention by enhancing physical interactions [5] the requirement for ADP has been well documented [4, 7] The results therefore support the hypothesis that ADP necessary for normal platelet retention to occur in glass bead columns is derived from red cells

The platelet retention was considerably reduced in the valve patients in spite of normal hemolysis related ADP liberation Why did not the ADP made available cause normal platelet retention? A tempting explanation is that the platelets were refractory because they were influenced by ADP appearing during continuous intravascular hemolysis as demonstrated in rabbits by water infusions [13] The minimum concentrations of ADP that are required to induce refractoriness have not been established but the water infusions resulted in reduced retention only when a considerable acute hemolysis had developed [13] To induce refractoriness in vitro, ADP concentrations of 0 1 μM have been used [6]

The ADP measured in plasma from venous and arterial blood was most probably derived from blood cells during the sampling and the preparation of plasma and also from the few platelets that remained in spite of the two step centrifugation Thus proportionally more ADP than hemoglobin was found although ADP is rapidly eliminated from the circulation [1] and hemoglobin more slowly [30]

The calculations on the intravascular liberation of ADP from red cells have established that only very low concentrations could theoretically occur near the prosthetic valves Moreover, the rapid breakdown of ADP would prevent accumulation and make the time of contact with a limited number of platelets short It is therefore quite inconceivable that the ADP liberated by intravascular hemolysis could influence platelet behavior

Two other possible mechanisms for the disturbed platelet function in patients with prosthetic valves have also been discussed previously [1] Consumption of adhesive platelets by thrombus formation has been rejected while damage inflicted on the platelets by the prosthetic valve could explain all the phenomena observed The valve could reduce platelet adhesiveness by affecting their membranes, either by the impact of the ball or by the turbulence induced in the blood or it might disturb platelet function by other mechanisms Thus it has recently been demonstrated that platelets that have undergone release and aggregated after exposure to thrombin may disaggregate and survive in the circulation, and even have some hemostatic effect [31] It is therefore possible that the trauma might induce release to some extent, and leave platelets with a reduced functional ability in the blood Release could explain the raised plasma levels of platelet factor 4 found in some patients with prosthetic valves [3] Some ADP would then also be released but in far too small amounts to induce refractoriness in other platelets

In conclusion the reduced platelet adhesiveness in ball valve patients is most probably due to the effect of the prosthesis on the platelets themselves and is unlikely to be secondary to intravascular hemolysis

Summary

The whole blood content of ADP and ATP was normal in patients with prosthetic aortic ball valves in spite of increased red cell breakdown During passage of EDTA anticoagulated blood through glass bead columns a slight but quite constant degree of hemolysis was produced similar in blood from healthy individuals and ball valve patients The adenine nucleotides were liberated largely in the same proportions as hemoglobin and ADP appeared in mean concentrations of 0 10 μM in each group of subjects The results indicate that the ADP necessary for

Table I Prevalence of $TV_1 > TV_6$ in an otherwise normal electrocardiogram in cases and controls on the exam before the initial onset of clinical manifestation of coronary heart disease

Diagnosis	*Males*		*Females*	
	Prevalence in cases	*Prevalence in matched controls*	*Prevalence in cases*	*Prevalence in matched controls*
Angina pectoris	18/64 = [illegible]	[illegible] = [illegible]	[illegible] = [illegible]	10/[illegible] = 11%
Coronary insufficiency	6/13 = [illegible]	[illegible]/30 = [illegible]	0/11 = 0%	0/11 = 0%
Anterior myocardial infarction	8/33 = [illegible]	9/3[illegible] = [illegible]	1/13 = [illegible]	1/14 = [illegible]
True posterior myocardial infarction	[illegible] = [illegible]	0/[illegible] = 0%	0/1 = 0%	None
Inferior myocardial infarction	9/29 = 31%	11/3[illegible] = 34	1/[illegible] = 14%	0/6 = 0%
Myocardial infarction without electrocardiographic evidence	8/21 = 38%	8/[illegible]1 = 3[illegible]	1/[illegible] = 2[illegible]	0/6 = 0%
Non sudden death	5/19 = [illegible]	[illegible] = [illegible]	1/[illegible] = 1[illegible]	0/11 = 0%
Sudden death	9/[illegible] = 3[illegible]	13/3[illegible] = 3[illegible]	0/[illegible] = 0%	0/[illegible] = 0%
Totals	65/[illegible]14 = 30%	6[illegible] = 2[illegible]	10/130 = [illegible]	11/144 = [illegible]

Table II Prevalence of $TV_1 > TV_6$ in an otherwise normal electrocardiogram in cases and controls on the exam after the initial onset of clinical manifestations of coronary heart disease

Diagnosis	*Males*		*Females*	
	Prevalence in cases	*Prevalence in matched controls*	*Prevalence in cases*	*Prevalence in matched controls*
Angina pectoris	1[illegible]/[illegible]8 = 1[illegible]	13/65 = [illegible]	9/62 = 1[illegible]	10/8[illegible] = 1[illegible]
Coronary insufficiency	3/6 = [illegible]	[illegible]/1[illegible] = 41%	0/[illegible] = 0%	1/1[illegible] = [illegible]
Myocardial infarction without electrocardiographic evidence	8/14 = 5[illegible]	6/[illegible] = [illegible]	0/4 = 0%	0/6 = 0%
Totals	[illegible]3/[illegible]8 = [illegible]	[illegible]6/103 = [illegible]	[illegible]/[illegible]3 = 1[illegible]	11/103 = 11%

upright while the T wave in V_1 could either be upright, flat, or inverted.

Since certain non-cardiac characteristics such as blood pressure level, relative weight, and cigarette smoking status may play a role in predisposing to coronary heart disease as well as in producing this electrocardiographic pattern, information regarding these factors was recorded for all cases and controls.

Results

Among all those who would go on to develop a clinical manifestation of coronary heart disease, 214 of 323 (66 per cent) of the males and 131 of 195 (67 per cent) of the females had normal electrocardiographic tracings on the Framingham exam immediately preceding its onset. Of the controls, 72 per cent had a normal tracing on the corresponding exam. Data concerning the ability of $TV_1 > TV_6$ in an otherwise normal electrocardiogram to detect impending clinical coronary heart disease are given in Table I. As had been previously reported by Teichholz and associates,[4] $TV_1 > TV_6$ was found to be far more prevalent in males than in females. Consequently, all the analyses were done separately for males and females. In individuals with otherwise normal electrocardiograms, there was no significant difference between the cases and the controls in the prevalence of $TV_1 > TV_6$ on the exam before the onset of clinical disease. This was true for all five designated categories of coronary disease in both males and females.

Among individuals diagnosed as having angina pectoris or coronary insufficiency, 64 of 123 (52 per cent) of the males and 69 of 137 (50 per cent) of the females had normal electrocardiograms on the first Framingham exam after the initial onset

Precordial T wave vectors in the detection of coronary heart disease The Framingham Study

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It is well known that resting electrocardiographic aberrancy is often absent in persons soon to develop clinically overt coronary heart disease In addition a significant percentage of people diagnosed as having angina pectoris have entirely normal resting electrocardiographic tracings [1] It would therefore, be of great value if some pattern within the normal' resting electrocardiographic tracing could be identified that would either aid in detecting impending clinical coronary heart disease or in confirming coronary heart disease in the presence of clinical symptoms Several reports have claimed an association between an anteriorly oriented precordial T wave vector and various anatomic and clinical parameters of coronary heart disease [*] In these reports a T wave amplitude in V_1 greater than that in V_6 ($TV_1 > TV_6$) was utilized as the electrocardiographic expression of an anteriorly oriented precordial T wave vector If the pattern of $TV_1 > TV_6$ in an otherwise normal electrocardiographic tracing is truly an indicator of ischemic changes in the myocardium it might then be a reliable detector of the presence of impending clinical coronary heart disease It might also prove to be a useful adjunct in the diagnostic evaluation of patients with chest pain A case-control study utilizing the epidemiologic data of the Framingham Heart Study was designed to test this hypothesis

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Material and methods

The case population consisted of 518 people (323 males, 195 females) who had developed coronary heart disease between 1948 and 1968 while under observation by the Framingham Heart Study Program Each was characterized according to the initial clinical manifestation of the disease as defined by Framingham criteria i.e angina pectoris coronary insufficiency myocardial infarction sudden death and non sudden death [7] Each case was matched with a control by age, sex and Framingham exam number on which the case s diagnosis of coronary heart disease was first made Each control was drawn from the Framingham Heart Study cohort that had never manifested any clinical evidence of coronary heart disease from 1948 through 1968 Data from the routine Framingham Heart Study biennial exams which immediately preceded and followed the initial clinical manifestations of coronary disease were evaluated for each member of the case population Data from corresponding exam numbers were evaluated for each matched control All electrocardiographic tracings were recorded on a standard twelve lead Sanborn visocardiette with the subject in the recumbent position Criteria used to designate the tracing as normal or abnormal were consistent with those previously outlined The amplitudes of TV_1 and TV_6 were determined with a standard electrocardiographic caliper by measuring on a line perpendicular to a continuation of the TP segment the vertical distance between the TP segment and the peak of the T wave TV_1 had to be at least one half millimeter greater in amplitude than TV_6 before a designation of $TV_1 > TV_6$ could be made In order to be considered within the category of normal T waves the T wave in V had to be

Table I Prevalence of $TV_1 > TV$ in an otherwise normal electrocardiogram in cases and controls on the exam before the initial onset of clinical manifestation of coronary heart disease

Diagnosis	Males		Females	
	Prevalence in cases	*Prevalence in matched controls*	*Prevalence in cases*	*Prevalence in matched controls*
Angina pectoris	18/64 = [illegible]	1[illegible] = [illegible]	[illegible]/82 = [illegible]	10/90 = 11
Coronary insufficiency	6/13 = 46%	[illegible]/90 = 3[illegible]	0/11 = 0%	0/11 = 0%
Anterior myocardial infarction	8/33 = 24%	9/3[illegible] = 2[illegible]	1/13 = [illegible]	1/14 = [illegible]
True posterior myocardial infarction	2/7 = [illegible]	0/[illegible] = 0%	0/1 = 0%	None
Inferior myocardial infarction	9/[illegible] = 31%	11/3[illegible] = 3[illegible]	1/[illegible] = 14%	0/6 = 0%
Myocardial infarction without electrocardiographic evidence	8/[illegible] = [illegible]	8/21 = 3[illegible]	1/[illegible] = 20%	0/[illegible] = 0%
Non sudden death	5/19 = [illegible]	[illegible] = [illegible]	1/6 = 1[illegible]	0/11 = 0%
Sudden death	9/[illegible]8 = 3[illegible]	13/3[illegible] = 3[illegible]	0/6 = 0%	0/[illegible] = 0%
Totals	6[illegible]/214 = 3[illegible]	[illegible] = [illegible]	10/130 = [illegible]	11/141 = [illegible]

Table II Prevalence of $TV > TV$ in an otherwise normal electrocardiogram in cases and controls on the exam after the initial onset of clinical manifestations of coronary heart disease

Diagnosis	Males		Female	
	Prevalence in cases	*Prevalence in matched control*	*Prevalence in case*	*Prevalence in matched controls*
Angina pectoris	1[illegible]/[illegible]8 = 1[illegible]	13/65 = 20%	9/6[illegible] = 14%	10/8[illegible] = 12%
Coronary insufficiency	3/[illegible] = [illegible]	[illegible]/1[illegible] = 41%	0 = 0%	1/1[illegible] = 8%
Myocardial infarction without electrocardiographic evidence	8/14 = 5[illegible]	6/21 = 2[illegible]	0/4 = 0%	0/6 = 0%
Totals	23/[illegible]8 = [illegible]	[illegible]/103 = [illegible]	[illegible]/73 = 1[illegible]	11/103 = 11%

upright while the T wave in V_1 could either be upright flat or inverted

Since certain non cardiac characteristics such as blood pressure level relative weight and cigarette smoking status may play a role in predisposing to coronary heart disease as well as in producing this electrocardiographic pattern information regarding these factors was recorded for all cases and controls

Results

Among all those who would go on to develop a clinical manifestation of coronary heart disease 214 of 323 (66 per cent) of the males and 131 of 195 (67 per cent) of the females had normal electrocardiographic tracings on the Framingham exam immediately preceding its onset Of the controls 72 per cent had a normal tracing on the corresponding exam Data concerning the ability of $TV > TV$ in an otherwise normal electrocardiogram to detect impending clinical coronary heart disease are given in Table I As had been previously reported by Teichholz and associates $TV > TV$ was found to be far more prevalent in males than in females Consequently all the analyses were done separately for males and females In individuals with otherwise normal electrocardiograms there was no significant difference between the cases and the controls in the prevalence of $TV > TV$ on the exam before the onset of clinical disease This was true for all five designated categories of coronary disease in both males and females

Among individuals diagnosed as having angina pectoris or coronary insufficiency 64 of 123 (52 per cent) of the males and 69 of 137 (50 per cent) of the females had normal electrocardiograms on the first Framingham exam after the initial onset

Table III Percentage of cases and controls with normal electrocardiograms on both the exam before and the exam after the initial onset of clinical manifestations of coronary heart disease that go from a $TV_1 < TV_6$ on the first exam to a $TV_1 > TV_6$ on the second exam

	Males		Females	
Finding	*Cases*	*Controls*	*Cases*	*Controls*
$TV < TV$ to $TV > TV_6$	7/43 = 16%	12/137 = 9%	4/57 = 7%	5/109 = 5%

of clinical disease Of the individuals who developed clinically documented myocardial infarctions 18 of 155 (12 per cent) had electrocardiographic tracings that were entirely normal on the first Framingham exam after the event Table II shows that in individuals with otherwise normal electrocardiograms there was again no significant difference between the cases and the controls in the prevalence of $TV_1 > TV_6$ on the exam after the initial clinical manifestations of coronary disease appeared From Table II it can be calculated that in males $TV_1 > TV_6$ had a sensitivity of only 29 per cent, a specificity of 47 per cent, and a false positivity of 25 per cent in detecting the presence of overt coronary heart disease These values differ markedly from those reported by Okomoto and colleagues[5] and by Teichholz and associates [6]

The incidence of conversion from a $TV_1 < TV_6$ on the exam preceding the onset of clinical coronary heart disease to a $TV_1 > TV_6$ on the exam following the development of disease in cases and controls with normal electrocardiograms on both exams is illustrated in Table III In both males and females conversion from $TV_1 < TV_6$ on the first exam to a $TV_1 > TV_6$ on the second exam although almost twice as common in cases than in controls was not significant to $p < 0.05$

$TV_1 > TV_6$ was far more prevalent among people listed as having non specific or possible non specific T wave changes than among people with otherwise normal electrocardiograms However, among people with definite or possible non specific T wave changes on the exam before the onset of clinical disease the ratio of the number of people with $TV_1 > TV_6$ to the number of people with $TV_1 < TV_6$ was not significantly different in the cases than in the controls Likewise, among people with definite or possible non specific T wave changes on the exam after overt disease first appeared the ratio of the number of people with $TV_1 > TV_6$ to the number of people with $TV_1 < TV_6$ was again not significantly different in the cases than in the controls

In neither cases nor controls with normal electrocardiograms was there a relationship between the prevalence of $TV_1 > TV_6$ and the individuals age relative weight cigarette smoking habits o electrocardiographic frontal plane axis This wa true for both males and females In male controls there was an increasing prevalence of $TV_1 > TV$ with increasing blood pressure levels ($p < 0.0$ There was no correlation however, between th prevalence of $TV_1 > TV_6$ and blood pressur levels in male cases, or in female cases o controls

Discussion

The absence of resting electrocardiograph aberrancy in two thirds of the Framinghan subjects soon to develop clinical coronary hear disease and in half of the Framingham subject with documented angina attests to the insensi tivity of the standard electrocardiographic abnor malities in detecting incipient or overt clinica coronary disease These observations justify the search for other electrocardiographic pattern within the normal tracing which might indicate the presence of ventricular ischemia Meyer and Herr and Arustamov[3] associated a finding of $TV_1 > TV$ with various causes of delayed left ventricular repolarization such as left ventricula hypertrophy or coronary insufficiency Weyn and Marriott[4] stated that the importance o $TV_1 > TV$ lay in its potential to indicat ischemic or hypertensive myocardial abnormali ties in the presence of an otherwise normal elec trocardiogram Okomoto and colleagues[5] exam ined the electrocardiograms of 500 males diag nosed as having angina pectoris myocardia infarction hypertensive, pulmonary or valvula heart disease and 960 unmatched control without clinical evidence of heart disease When they considered only subjects with otherwise normal electrocardiograms with positive T waves in V TV > TV_6 was approximately 60 per cent sensitive in detecting the presence of cardiac disease with 22 per cent false positives Teichholz and associates[6] studied the relevance o

$TV_1 > TV$ angiographically in 179 patients with chest pain syndromes and otherwise normal electrocardiograms. Their results in males indicated a 46 per cent sensitivity and a 90 per cent specificity in the ability of $TV_1 > TV$ to diagnose coronary artery disease in the presence of chest pain syndromes. Grant has stated that delayed left ventricular repolarization will tend to rotate the precordial T wave vector anteriorly. This is the mechanism he invokes to explain how left ventricular ischemia might lead to an anteriorly oriented T wave vector. Previous investigators chose $TV > TV_6$ simply as a reference point which they believed defined a T wave vector sufficiently anteriorly oriented to indicate the presence of left ventricular ischemia.

To the best of our knowledge this is the first report that presents data that run contrary to previous data concerning the diagnostic significance of an anteriorly oriented precordial T wave vector in an otherwise normal electrocardiogram. The presence of generalized non-specific ST and T abnormalities on an individual's electrocardiogram has been shown by the Framingham Heart Study to impart approximately a twofold increased risk for the subsequent development of clinical coronary heart disease. However, the accuracy of utilizing changes in T wave morphology as a diagnostic tool in the detection of coronary heart disease is limited by the large number of physiologic conditions other than ischemia that can alter the amplitude and direction of the T wave. Some of these factors might have contributed both to the low prevalence of an anterior T wave vector in the case population in this study and to the high prevalence in the controls. The results of this study, however, indicate that subsequent development of clinical coronary disease in people with normal electrocardiograms is unrelated to $TV > TV$ as an antecedent finding. Furthermore, this study demonstrates that in people with clinical evidence of coronary heart disease and normal electrocardiograms, $TV > TV$ fulfills neither the criterion for a good screening test (high sensitivity) nor the criterion for a good diagnostic test (high specificity). In addition, $TV > TV$ was not able to add to the specificity of generalized non-specific T wave changes in detecting the people with either preclinical or overt coronary heart disease.

Methodological differences between this study and the others, such as the patient selection, definition of disease, and the composition of the control groups, can be invoked to account for the divergent findings. All the previous studies utilized various selective processes to assemble their patient populations. This study drew its cases and controls from a representative population sample which contained within it all the people who developed coronary heart disease and all the people with the $TV > TV$ phenomenon. It is certain that if a T wave amplitude in V_1 greater than that in V_6 in an otherwise normal electrocardiogram was truly a result of coronary heart disease, its prevalence should have been significantly greater in a large group of people with clinical coronary heart disease than in a control group of people known to be free from clinical coronary heart disease, matched for age and sex, and drawn from the same unselected general population sample.

Summary

An anteriorly oriented precordial T wave vector manifested by a T wave amplitude in V greater than that in V ($TV > TV$) has been reported to be a useful criterion for the detection of coronary heart disease in people with otherwise normal electrocardiograms. In an effort to confirm this observation, a prospective case-control study based on 518 subjects who developed clinical coronary heart disease while under observation by the Framingham Heart Study and 518 age- and sex-matched controls free from coronary heart disease was carried out. Analysis of electrocardiograms considered to be normal and obtained at routine biennial exams revealed that on the exam prior to the onset of clinical coronary heart disease there was no significant difference in the prevalence of $TV > TV$ between people who subsequently went on to develop disease and the controls. Furthermore, no significant difference in the prevalence of $TV > TV$ was noted between cases and controls on the first exam following the initial clinical manifestations of coronary heart disease. When studied prospectively in the general population, the data indicate that $TV > TV$ in an otherwise normal electrocardiogram is not sufficiently specific a discriminator to be utilized as a reliable criterion for the detection of coronary heart disease.

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Angina pectoris and intermittent claudication

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Angina pectoris and intermittent claudication are both manifestations of transient ischemia to cardiac and skeletal muscle respectively brought on by exertion and relieved by rest In the majority of cases atherosclerosis appears to be the pathologic basis for both angina pectoris and intermittent claudication Patients with intermittent claudication have both a propensity for developing ischemic heart disease and an increased risk of dying from cardiovascular disease Thus in any patient population referred with angina pectoris it would not be unusual to find a subgroup of patients also having evidence of atherosclerosis of the femoral-popliteal artery system The purpose of the following report is to present a group of patients referred for evaluation of angina pectoris who also had clinical evidence of peripheral vascular disease of the lower extremities These patients will be compared with two other groups of patients one with only symptomatic coronary disease and a second without evidence of either coronary or peripheral vascular disea e

Methods

A review of 1 200 consecutive patients referred for evaluation of angina pectoris revealed 60 patients (5 per cent) with a prior history of intermittent claudication and diminished or absent pulses in the lower extremities These 60 patients form the ba is of thi report and were compared with two other groups of patients Group I con i ted of patients without clinical evidence of peripheral vascular disease and normal coronary arteriograms These patients were evaluated because of one of the following problems recurrent atypical chest pain abnormal electrocardiogram intractable arrhythmia or an unexplained heart murmur Group II consi ted of patients referred because of angina pectoris but without clinical evidence of peripheral vascular disease all had arteriographic evidence of coronary artery disease Patients in Group I and II were matched for both age and sex with the 60 patients having both coronary artery and peripheral vascular disease (Group III)

All patients were interviewed examined and evaluated by one of the authors (R I H A A) The hi tory included the duration of symptoms for both angina pectoris and intermittent claudication A history of a myocardial infarction was accepted if documented by the referring doctor or if the patient had a prior hospitalization for at least three weeks for prolonged chest pain A diagnosis of hypertension required either a history of antihypertensive therapy or a persistent diastolic pressure of 90 mm Hg or over when admitted for evaluation A positive history of cigarette smoking required consumption of 20 cigarettes or more per day for at least ten years prior to the onset of symptoms A diagnosis of diabetes mellitus required either a history of diabetes mellitus accompanied by an elevated fasting blood sugar on admission or if no known prior diagnosis was ever made an elevated fasting blood sugar on admission accompanied by glycos

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Table I Clinical profile of patients

	Group I	Group II (ASHD)*	Group III (ASHD + PVD)
Total number	60	60	60
Duration of symptoms (yrs ± 1 S.D.)			
Angina pectoris	–	3.1 ± 3.5	3.6 ± 3.9
Intermittent claudication	–	–	4.3 ± 3.6
Medical history			
Myocardial infarction (by history)	–	26 (43)†	26 (43)
Hypertension	14 (23)	18 (30)	23 (38)
Cigarette smoking	19 (32)	27 (45)	30 (50)
Diabetes mellitus	2 (3)‡	13 (22)	27 (45)
Family history			
Arteriosclerotic heart disease	26 (43)§	35 (58)	41 (68)
Hypertension	13 (22)	19 (32)	25 (42)
Diabetes mellitus	10 (16)§	11 (18)	22 (37)
Myocardial infarction (by ECG)	–	19 (32)	23 (38)
Cardiomegaly (by x-ray)	–	8 (13)	12 (20)

*ASHD = arteriosclerotic heart disease. PVD = peripheral vascular disease.
†Numbers in parenthesis represent the per cent for each group.
‡When Group I compared to Group II $p < 0.005$; when Group I compared with Group III $p < 0.001$; when Group II compared to Group III $p < 0.01$.
§When Group I compared to Group III $p < 0.01$.

uria. On admission, each patient was closely questioned as to a family history in first generation relatives of arteriosclerotic heart disease, hypertension, or diabetes mellitus. A twelve lead standard electrocardiogram was taken on all patients and was interpreted on the basis of accepted criteria. Chest radiologic evaluation and interpretation was performed by a radiologist to define the presence or absence of cardiomegaly. After a 12- to 16-hour fast and discontinuation of all medication, blood was drawn in the morning for a glucose tolerance test and lipid studies. Serum cholesterol was determined using an autoanalyzer and serum triglyceride was determined by a modification of the method described by Solomon.[4] For both cholesterol and triglyceride an abnormal value was defined as that value above a recommended age-adjusted normal range as recommended by Fredrickson.

All patients underwent complete cardiac catheterization and selective coronary arteriographic studies by methods previously described. Selective coronary angiograms were reviewed and each of the three major coronary arteries were graded on the basis of score from 0 to 6 as previously described[6] and defined by Bruschke. The total coronary score, used as an indicator of the severity of the coronary artery disease, was the sum of the score of the three major coronary arteries. Involvement of the main left coronary artery was considered separately. Significant coronary artery disease was defined as narrowing of a coronary artery by more than 50 per cent of the lumen. Single vessel disease was defined as significant coronary artery disease of only one vessel, while double and triple vessel disease indicated significant disease of two or three coronary arteries, respectively. Follow-up after coronary surgery was obtained by office visit or by telephone. Statistical evaluation of all the data was obtained by the two-tailed Student's t test for unpaired data and χ^2 test[9] with the assistance of a statistician.

Results

Each of the three groups, matched for both age and sex, consisted of 49 male and 11 female patients. The average age of the male and female patients was 56 ± 8.4 and 60 ± 8.5 years, respectively. The ages of the patients ranged from 37 to 75 years with 80 per cent of the patients 50 years or over. Seven patients were 70 years or older. A comparison of the clinical profile of the three groups of patients is shown in Table I. The frequency of hypertension or cigarette smoking revealed no significant differences when all three groups were compared with each other. The frequency of diabetes mellitus was significantly higher in both Group II ($p < 0.005$) and III ($p < 0.001$) when compared to Group I. Furthermore, in Group III 45 per cent of the patients had diabetes mellitus, significantly higher than the frequency in Group II. The frequency of a family history of arteriosclerotic heart disease ($p < 0.01$), diabetes mellitus ($p < 0.01$), and hypertension ($p < 0.025$) was higher in Group III than Group I (Table I).

Intermittent claudication, which was present only in Group III, preceded angina pectoris in 4[illegible] patients (68 per cent). One of these patients had history of a lumbar sympathectomy and two patients had previous femoral-popliteal bypass surgery. Almost uniformly, with the onset of exertional angina pectoris the intermittent claudication caused either no functional disability o[illegible]

showed no progression In the 19 patients with the intermittent claudication developing after the onset of angina pectoris the functional disability was due predominantly to the angina pectoris

The serum cholesterol for Groups II and III were 246 ± and 46 and 259 ± 47 mg per cent respectively which are significantly higher ($p < 0\ 01$) than 203 ± 36 mg per cent observed in Group I Thirteen per cent of the patients in both Group II and III had an abnormal cholesterol as compared to 4 per cent noted in Group I The serum triglyceride for Group II and III were 177 ± 87 and 176 ± 93 mg per cent which was significantly higher ($p < 0\ 01$) than 134 ± 64 mg per cent found in Group I The frequency of an abnormal triglyceride in Group II and III were 38 and 47 per cent respectively as compared to 11 per cent in Group I

Comparing Group II and III in respect to the number of vessels involved with significant coronary artery disease and the total coronary score revealed no significant differences (Table II) On the basis of the functional status of the patient together with the coronary anatomy and left ventricular function aortocoronary bypass surgery was performed on 48 and 47 patients in Group II and III respectively The number of grafts placed at the time of surgery and the postoperative course were comparable in both groups Only one patient died at surgery in Group III In the remaining patients in both of these groups surgery was not performed for several reasons (Table III) including poor left ventricular function diffuse coronary artery disease infarction or expiration while waiting for surgery or insufficient disease judged not to warrant bypass Postoperative follow up revealed functional cardiac improvement in the majority of patients in both groups (Table III) Of the 43 patients in Group III functional deterioration on follow up due to intermittent claudication was observed in 12 patients (28 per cent) In six of these patients surgery was performed six to 24 months after coronary surgery and included lumbar sympathectomy in one femoral popliteal bypass in four and amputation in one patient

Discussion

The pathophysiologic basis of both angina pectoris and intermittent claudication are remarkably similar Both clinical conditions are usually manifested on exertion as a result of atheromatous changes in the arterial system Both are related to transient ischemia which may be relieved by rest The Framingham Study[2] indicated that the risk of one of these ischemic clinical states is increased by the presence of the other In the Framingham Study men with preexisting angina pectoris had almost three times and women had five times the risk of developing intermittent claudication when compared to a population not having evidence of ischemic heart disease In a similar manner patients with preexisting intermittent claudication were found to have a pronounced increased risk of developing angina pectoris Such a relationship suggests a

Table II Coronary artery anatomy

	Group II	*Group III*
Number of vessels involved		
Single	11	10
Double	22	21
Triple	[illegible]	[illegible]
Main left coronary disease	4	[illegible]
Total coronary artery score (mean ± 1 S D)	100 ± 2 8	[illegible]

Table III Surgery and follow up

	Group II	*Group III*
Aortocoronary bypass surgery	48	4
Surgical mortality	0	1
Coronary surgery not performed	1	13
Poor left ventricular function and/or diffuse coronary artery disease	8	[illegible]
Infarction or expired waiting for surgery	1	[illegible]
Surgery not recommended for single vessel disease of right coronary or circumflex artery	3	2
Postoperative follow-up (mean range)	[illegible]	[illegible]
Number followed	4[illegible]	43
Cardiac status		
Improved	38	40
Unchanged	3	1
Worse	1	
Intermittent claudication		-
Improved		
Unchanged		3
Worse		[illegible]8
		12

common etiologic basis for both peripheral vascular and coronary artery disease In studies devoted to patients with peripheral vascular disease, the frequency of coexisting coronary disease varied from 16 to 29 per cent[9, 11] In the present study of a patient population referred for ischemic heart disease the frequency of intermittent claudication was observed to be five per cent This frequency cannot be used as representative of the true frequency of intermittent claudication with angina pectoris since the patients in the present study represent a select group referred primarily because of disabling symptoms of angina pectoris Furthermore, it is quite conceivable that pre existing intermittent claudication will limit and protect against the functional restriction that angina pectoris would otherwise have brought on In the present study in almost two thirds of the patients the clinical manifestations of peripheral vascular disease preceded those of coronary artery disease In three of these patients surgical intervention (lumbar sympathectomy in one and femoral popliteal bypass in two) was required because of major restrictions as a result of the peripheral vascular disease In the majority of patients once the symptoms of coronary artery disease developed the intermittent claudication caused only minor disability It is apparent that the physical restriction brought on by angina pectoris resulted in a limited protection from the compromised circulation in the lower extremities It was not uncommon for a patient to note significant improvement in the anginal status as a result of medication only to find himself limited by exertional cramps in his legs This is further exemplified by the events that occurred after aortocoronary bypass surgery In almost 30 per cent of the patients the intermittent claudication was reported on follow up to have worsened, necessitating some form of surgery in six patients Thus the alleviation of the myocardial ischemic symptoms from the coronary artery disease permitting an increased functional tolerance unmasked the compromised circulation to the lower extremities

The patients with both coronary artery and peripheral vascular disease (Group III) were compared to patients also referred for angina pectoris but not having peripheral vascular disease (Group II), in order to determine whether there were any distinct characteristics other than intermittent claudication which could distinguish one group from the other Furthermore both of the groups with angina pectoris were compared with an age and sex matched control group (Group I) that had neither evidence of peripheral or coronary artery disease in order to determine whether the factors evaluated were simply characteristic of any patient population of similar age and sex having arteriosclerotic heart disease Epidemiologic studies[1, 13] have indicated that both hypertension and cigarette smoking are distinct risk factors for the occurrence of coronary artery disease Similar types of epidemiologic studies on peripheral vascular disease are not available In the present study both of these factors were more frequent in the patients with coronary artery disease (Group II and III), as compared to the control group (Group I) however the differences were not statistically significant (Table I) Diabetes mellitus appeared to be the one factor which distinguished patients with peripheral vascular disease from both groups of patients with no evidence of peripheral vascular disease (Table I) Furthermore the frequency of diabetes mellitus in both groups with coronary artery disease (Groups II and III) was significantly higher than the group of patients without coronary artery disease The association of coronary artery disease[14, 16] and peripheral vascular disease[14, 1, 18] with diabetes mellitus has been well documented The present study confirms these observations and indicate that the diabetic patient has an increased risk of clinically developing simultaneously both coronary artery and peripheral vascular disease A comparative review of all three groups of patients for a family history of coronary artery disease hypertension and diabetes mellitus revealed no significant differences between the two groups with angina pectoris However comparing the angina pectoris patients who also had peripheral vascular disease with the control group revealed an increased frequency of a family history of arteriosclerotic heart disease ($p < 0.01$) and hypertension ($p < 0.025$) Serum cholesterol and triglyceride were significantly higher in both of the groups with coronary artery disease as compared to the control group Neither cholesterol nor triglyceride levels distinguished the patients having only angina pectoris from those having intermittent claudication as well The lipid studies reported by Greenhalgh and co workers[1] on patients with peripheral vascular

disease are comparable to those found in both groups of the present study with coronary artery disease. In that study, an abnormal cholesterol level was observed in 14.5 per cent of the patients as compared to 13 per cent in Group II and III of the present study. An elevated triglyceride level was present in 39.5 per cent of the patients in Greenhalgh's series, as compared to 38 and 47 per cent in Group II and III, respectively. In the study of Vyden and associates of patients with peripheral vascular disease, 50 per cent had an elevated serum triglyceride level, whereas the serum cholesterol levels were similar to a control group. These studies, as well as those on patients with coronary artery disease,[11] suggest an important role of abnormal serum triglyceride level in the pathogenesis of atherosclerosis.

This study demonstrates that the severity of the coronary artery disease as reflected by either the number of vessels involved with significant disease or the coronary artery score (Table II) was in no way different in patients with intermittent claudication and angina pectoris when compared to a group of patients matched for age and sex having only coronary artery disease. The number of patients undergoing aortocoronary bypass surgery, number of grafts placed at the time of surgery, postoperative course and follow-up of their cardiac status were comparable in both groups. Thus, it is apparent that peripheral vascular disease of the lower extremities in a patient with coronary artery disease should not interdict coronary revascularization if clinically warranted. However, as indicated by our follow-up experience, the patient should understand that clinical improvement in the cardiac status may be accompanied by recurrence or apparent deterioration of the vascular insufficiency in the lower extremities. If such a course of events does occur, consideration may be required for surgical revascularization in the lower extremities.

Summary

Sixty patients referred for angina pectoris and having coexisting intermittent claudication (Group III) were compared with two groups of patients matched for both age and sex. One group (Group I) had no evidence of either coronary or peripheral vascular disease, while Group II had only symptomatic coronary artery disease. The ages of the patients ranged from 37 to 75 years with 60 per cent of the patients 50 years or over. In Group III, intermittent claudication preceded the development of angina pectoris in 41 patients (68 per cent) and with the onset of exertional angina pectoris, the intermittent claudication usually caused no major disability. The frequency of hypertension and cigarette smoking was not different when all three groups were compared. Diabetes mellitus was significantly higher in both Group II ($p < 0.005$) and Group III ($p < 0.001$) than in Group I. In Group III, 45 per cent of the patients had diabetes mellitus as compared to 22 per cent in Group II ($p < 0.01$). The frequency of a family history of arteriosclerotic heart disease ($p < 0.01$), diabetes mellitus ($p < 0.01$), and hypertension ($p < 0.025$) was higher in Group III as compared to Group I. Serum cholesterol and triglyceride comparison revealed no differences between Groups II and III, but both groups were significantly higher ($p < 0.01$) as compared to Group I. The severity of coronary artery disease as reflected by the number of vessels involved and coronary artery score were similar in both Group II and III. The number of patients operated on for coronary surgery, number of grafts required, postoperative course and follow-up of their cardiac status was similar for both Group II and III. In 12 of 43 patients followed in Group III, a recurrence or apparent deterioration of the vascular insufficiency in the lower extremities required surgery in six patients. Thus, peripheral vascular disease of the lower extremities should not be a deterrent against recommending a patient for coronary surgery if otherwise clinically warranted.

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The effect of respiration on normal and abnormal Q waves

An Electrocardiographic and Vectorcardiographic Analysis

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Recent investigations have refined the vectorcardiographic (VCG) criteria for diagnosis of inferior infarction and determined the limitation of electrocardiographic (ECG) sensitivity However the presence of Q waves on the conventional scalar ECG remains the most widely used criterion for the diagnosis of myocardial infarction The difficulty encountered with the interpretation of the scalar ECG is particularly emphasized in the diagnosis of inferior myocardial infarction One study of the diagnostic value of the Q wave in patients with inferior myocardial infarction noted that 27 per cent manifested a Q in Lead 3 only Other authors consider that a Q3 even with a duration of 40 msec remains equivocal evidence for inferior infarction In addition it is well known that Q waves of short duration unassociated with myocardial infarction may be seen when the heart is in a vertical position or when the resultant axis is shifted to the right

Lyle in 1943 observed that inspiration causes a Q3 to diminish or disappear among normal subjects and to persist among patients with inferior infarction Deep inspiration was suggested therefore as a maneuver to differentiate a nonpathological Q3 from that caused by infarction Most of the studies in the past which assessed the effect of respiration on the Q wave in ECG Lead 2, 3 and aV$_F$ as a means of determining whether inferior infarction is present have been somewhat inadequate First the diagnosis of myocardial infarction was often made retrospectively based on history alone or on angiographic data It is imperative that the diagnosis of myocardial infarction be based on specific biochemical markers rather than on the ECG criterion which itself is being evaluated Furthermore studies should be performed prospectively both at the time of infarction and some time later such as 6 to 12 months after infarction Secondly all studies in the past employed only the ECG It is now well recognized that the VCG is a more sensitive and definitive means of detecting inferior infarction and therefore offers a specific advantage in assessing the diminutive Q wave on the scalar ECG

In view of these limitations and because of common acceptance of the validity of Lyle's observation a prospective study was undertaken to determine the effect of respiration on Q waves in Lead 3 utilizing both electrocardiographic and vectorcardiographic analysis The study included 55 patients 33 with documented myocardial infarction and 22 normal volunteers The diagnosis of myocardial infarction was based on serial ECG changes and serial enzyme elevation as well as elevated MB CPK (a CPK isoenzyme virtually specific for myocardium) The normal population was under the age of 30 and in good health

Methods

Selection of patients Thirty three patients with acute inferior myocardial infarction (Group 1) were selected from patients admitted to the Cardiac Care Unit at Barnes Hospital The diag

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Table II The effect of inspiration on the Q wave in Lead 3 of the electrocardiogram

	Number	Measurable Q	Change in Q wave amplitude		
			Decrease	Increase	No effect
(1A) Inferior infarction (new)	17	17	14	0	3
(1B) Inferior infarction (old)	16	16	6	1	9
(2A) Normal with superior force	15	8	1	0	-

frontal view was obtained on full inspiration and during full expiration. A calibration of 1 mv. per 2 cm. or 4 cm. deflection was used depending on the size of the total VCG loop. The initial QRS forces were enlarged with a calibration of 1 mv. per 10 cm. deflection and photographed with the P loop excluded. The VCG trace was interrupted each 2.5 msec. VCGs were recorded within two weeks after infarction in Group 1A and within 6 to 12 months in Group 1B. Manual measurements were made from the Polaroid prints of the VCG loops after magnification by hand lens.

The frontal plane VCG for both inspiration and expiration was analyzed for the initial 30 msec. of the VCG loop. The analysis was performed by first dividing each 30 msec. loop into 5 msec. intervals with a resultant division of six segments corresponding to a range from 5 to 30 msec. Each 5 msec. interval was established by placing a mark at the precise point corresponding to that duration on the VCG loop. At each 5 msec. interval mark, two parameters were measured: (1) the distance (mv.) from the 0 point of the VCG loop to the interval mark and (2) the angle from the 0 point to the interval mark. By convention the X axis was considered an angle of zero. Consequently, a superior force in the frontal plane would manifest a negative angle (range −1 to −180 degrees) and an inferior force would be recorded as positive angle (range +1 to +180 degrees). The inspiratory azimuth was defined as the change in the angle (from the 0 point to the interval mark) which occurred between forced expiration and full inspiration.

In addition to the above measurements, the following parameters were measured to establish or exclude the VCG diagnosis of inferior infarction: (1) time from the 0 point to the point at which early superior forces cross the X axis, (2) distance (mv.) from the 0 point at which the early superior clockwise forces cross the X axis, (3) orientation (angle) of the maximal QRS vector, and (4) magnitude of the maximal superior clockwise forces and the ratio of maximal superior to maximal inferior forces.

The VCG criteria for inferior infarction are those established by Starr and colleagues[3] which require initial superior forces and one of the following: (1) time from the 0 point to leftward X intercept of at least 25 msec. and distance from the 0 point to leftward X intercept of at least 0.30 mv., (2) a maximal frontal plane QRS vector less than 15 degrees, or (3) a maximal superior deviation of at least 0.1 mv. and a ratio of maximal superior to inferior deviation of at least 1.5.

Results

The incidence and duration of Q waves in the various groups are summarized in Table I. Though all of the patients with infarction satisfied the VCG criterion for inferior infarction, the incidence of diagnostic Q waves (> .03 sec.) on scalar ECG is only 73 per cent. In the normal subjects, the presence of an initial superior force was determined by VCG and was present in 15 (Group 2A), but scalar ECG exhibited a superior force in only eight subjects. Seven normal subjects (Group 2B) exhibited no superior force either by VCG or ECG.

The effect of inspiration on the Q waves observed on scalar ECG is summarized in Table II. In the patients with recent infarction, 14 of 17 had some decrease in the amplitude of the Q wave but in no case did it disappear, and in three patients there was no change. In the patients with old infarction, 56 per cent had no change with inspiration, six had minimal decrease, and one had minimal increase. The normal subjects with small Q waves exhibited essentially no change.

The effect of inspiration on the initial 20 and 30 msec. vectors in the patients with recent infarction is illustrated in Fig. 1. The change in the

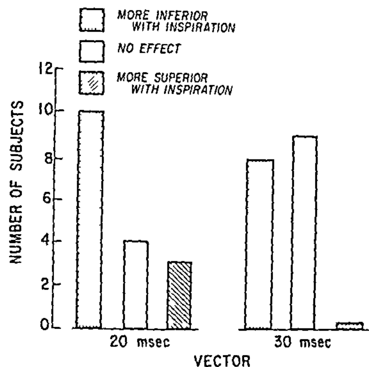


Fig 1 The effect of inspiration on the initial 20 msec and 30 msec vector of the vectorcardiogram in patients with acute inferior myocardial infarction

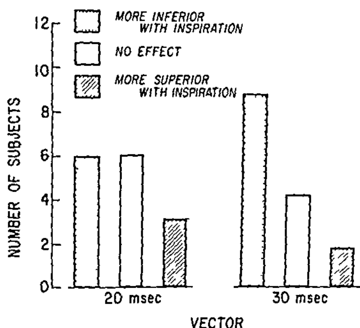


Fig 2 The effect of inspiration on the initial 20 msec and 30 msec vector of the vectorcardiogram in normal subjects

nosis of inferior infarction was based on the usual criterion of characteristic chest pain serial ECG changes with development of Q waves and serial changes in serum enzymes including elevated MB CPK [11] All patients in this group also satisfied the VCG criterion for inferior myocardial infarction The effects of respiration on Q waves were evaluated within two weeks of infarction in 17 patients

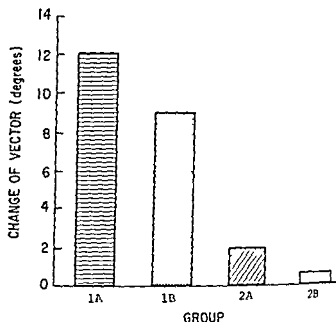


Fig 3 The mean change in orientation of the initial 20 msec vector of the vectorcardiogram with the difference be determined between full expiration and full inspiration

Table I The incidence and duration of the Q wave of electrocardiogram

Group	*No*	*Q wave ≥ 04*	*Q wave ≤ 03*
(1A) Inferior infarction (new)	17	10	[illegible]
(1B) Inferior infarction (old)	16	14	2
(2A) Normal with superior forces	15	0	6
(2B) Normal with no superior forces	7	0	0

(Group 1A) and 6 to 12 months after infarction in 16 patients (Group 1B) Group 2 consisted of normal volunteers

ECG and VCG analysis Standard 12 lead ECGs were recorded in the supine position and Leads 2 3 and aV_F were recorded during full inspiration and forced expiration The Q wave duration in Leads 2 3 and aV_F was measured to the nearest 01 sec interval in all ECGs The amplitude (depth) of the Q wave was also measured to the nearest 0 5 mv The VCGs were recorded using the Frank lead system on a Hewlett Packard Model 1507A vectorcardiograph and photographs of the frontal horizontal and left sagittal planes were taken from the oscilloscope screen on Polaroid Type 107 film A

analyzed on ECG is not a reliable method for the separation of normal from abnormal Q waves.

VCG was utilized in this study as an adjunctive method for the diagnosis of inferior infarction and for definition of a superior vector occurring among some normal subjects. In addition, the VCG provides a means of assessing the effect of inspiration on the initial 20 msec or 30 msec vector. Among the patients with acute infarction inspiration was associated with a more inferior orientation of the 20 msec vector in 67 per cent. The mean change in the inspiratory azimuth of 12 degrees was most pronounced among this group of patients. This VCG trend parallels that noted by ECG for the same group, as 82 per cent had a diminished Q wave with inspiration. VCG data analyzed at 30 msec showed that all patients either had a more inferior inspiratory azimuth or manifested no change. Results from the patients with old inferior infarction revealed a similar trend with the exception that more patients had no change in either 20 msec or 30 msec vectors with inspiration. This finding also reveal a similarity to the trend noted on ECG. Though the normal group demonstrated a change in nine subjects, this mean variation in inspiratory azimuth was minimal as noted in Fig. 3. Hence VCG data demonstrated trends paralleling those noted by ECG. The more precise definition of the initial superior vector again demonstrated that inspiration failed to appreciably change the 20 msec vector of normal subjects. Inspiration was associated with a trend of inferior orientation of the initial vector in patients with both acute and old inferior infarction.

In summary, this study provides an assessment of the effect of respiration on the Q wave of the scalar ECG in patients with inferior infarction and among normal subjects. VCG analysis was shown to be a more sensitive means of defining the initial superior vector and in documentation of inferior infarction. In a prospective study of patients with acute inferior infarction, inspiration was associated with a more inferior orientation or no change of the initial vector in the majority of patients. A similar finding was noted for patients with old inferior infarction. Normal subjects routinely demonstrated no significant change in orientation of a superior initial vector when present. Both ECG and VCG data revealed a correspondence in defining these trends. A Q3 on ECG generally persists with inspiration in both normal and in patients with inferior infarction. These results suggest that inspiration does not appear to be an effective maneuver for differentiating the Q3 of a normal subject from the Q3 which may be associated with inferior infarction.

Summary

The diagnostic significance of Q waves in Leads II, III, and aV_F when analyzed retrospectively remains controversial. Persistence of the Q wave on inspiration is said to reflect inferior infarction. Studies in the past which have evaluated respiratory variation as a means to separate normal from abnormal Q waves were performed utilizing the ECG only, were often retrospective, and frequently there was inadequate documentation of myocardial infarction. The present study was performed prospectively and utilized both electrocardiographic and vectorcardiographic analysis of the first 30 msec vector before and after inspiration in 33 patients with documented acute myocardial infarction and in 22 normal volunteers. Inferior myocardial infarction was documented prospectively by ECG, VCG, by conventional enzymes, and by MB CPK. The VCG demonstrated increased sensitivity over that of the ECG, but the effect of inspiration noted on ECG and VCG was variable and extremely unreliable as a means of separating normal from abnormal Q waves.

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direction of the vector was determined by measuring the inspiratory azimuth as previously described (see Methods section) The 20 msec vector in the majority of patients (59 per cent) exhibited a more inferior orientation on inspiration Inspiration produced no effect in four patients and a more superior vector in three patients The 30 msec vector in the same patients showed either a more inferior orientation (eight patients) or no change (nine patients) A similar effect was seen in patients with old infarction

Results of VCG analysis in the normal subjects are illustrated in Fig 2 Although the ECG detected a Q in only eight subjects the VCG detected some initial superior force in 15 subjects Following inspiration the 20 msec vector was changed in nine subjects This change was minimal as noted in Fig 3 and in fact this change was detected in only one subject by ECG The change as detected by VCG, however was not consistent in any one direction since in six subjects it became more inferior and in three more superior No change was seen in six subjects The 30 msec vector exhibited a more inferior direction in nine subjects superior orientation in two and no change in 4 subjects

Discussion

The diagnosis of an old inferior myocardial infarction by scalar ECG depends on the presence of Q waves of 40 msec duration or greater in Leads 2 3 and aV_F [1] However even at the time of infarction the Q waves may be less than 40 msec and certainly with time the Q wave frequently becomes shorter in duration [1, 16] In addition Q waves may develop in Lead 3 or aV_F only Since normal individuals may exhibit Q waves of 20 to 30 msec in any or all of these leads it is often difficult to determine whether infarction has occurred based on ECG criterion alone While present biochemical parameters facilitate the diagnosis of acute infarction the retrospective diagnosis of a prior inferior infarction from ECG alone is frequently a problem Because of this dilemma attempts have been made to delineate abnormal Q waves from those occurring in normal individuals as a result of septal depolarization One maneuver suggested by Lyle is deep inspiration which purportedly causes the Q3 in normal subjects to diminish or disappear but has no effect when infarction is present This interpretation has gained widespread acceptance and is now commonly practiced [11]

A recent study [5] has questioned the validity of the effect of deep inspiration on Q3 as a means to separate normal septal forces from those of inferior infarction However the documentation of inferior infarction was made retrospectively or depended on angiographic data rather than on specific biochemical markers of infarction In the present study transmural inferior infarction was documented prospectively by elevated serum enzymes including elevated plasma MB CPK [11] as well as by VCG criterion The effect of deep inspiration was analyzed utilizing not only ECG but also VCG, which has been shown to be more sensitive and specific for the diagnosis of inferior infarction and advantageous in analyzing the duration of Q waves on ECG [1]

The observation that the VCG is more sensitive than the ECG in the diagnosis of inferior infarction was confirmed in this study as shown by the results in Table I In 33 patients with transmural inferior infarction the VCG criterion was satisfied in all cases but the ECG criterion was satisfied in only 24 patients The VCG was also more sensitive than the ECG in detecting an initial superior force in the normal subjects since a superior force was detected in 15 subjects by VCG but in only eight subjects by ECG Furthermore the diminished specificity of ECG for the differentiation of normal from abnormal Q waves is illustrated by the presence of a Q3 less than 40 msec in nine patients with inferior infarction These nine patients would not be effectively separated from eight normal subjects who also had a Q3 of 30 msec or less

The effect of inspiration on Q3 analyzed by either the VCG or ECG clearly did not separate Q3 associated with normal septal depolarization from that caused by infarction The effect of inspiration analyzed by scalar ECG showed that Q3 decreased on inspiration in 82 per cent of the patients with recent infarction and in 44 per cent of patients with old infarction In the normal subjects the Q3 decreased in amplitude on inspiration in only one subject and was unchanged in the others The duration of Q3 in both normal subjects and in patients with infarction remained unchanged with inspiration These results indicate as do those reported by Shettigar and associates [5] that inspiratory variation in Q3

Effects of intravenous verapamil on hemodynamics in patients with heart disease

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Verapamil† a papaverine derivative was introduced as a coronary vasodilator in 1962 and was subsequently found to have potent antiarrhythmic properties in experimental animals[2] and antianginal effects in man The antiarrhythmic actions of verapamil have now been confirmed in man[4,5] The drug is extremely effective in terminating acute episodes of supraventricular tachycardia when administered intravenously[7] and there is increasing evidence that it may become the agent of choice for the initial treatment of paroxysmal supraventricular tachycardia

The pharmacological properties of verapamil have been related to its specific property of calcium antagonism at the membranes of excitable tissues Its effects on smooth muscle may be responsible for its vasodilator properties in the coronary and peripheral vessels while the depression of the calcium mediated slow response by the drug in cardiac muscle has been considered to be the mechanism of its antiarrhythmic action The ability of verapamil to inhibit the inward displacement of calcium ions across cardiac cell membranes must affect excitation-contraction coupling with resulting negative inotropic actions, as has been confirmed in isolated muscle[8] The overall cardiovascular actions of verapamil are therefore of therapeutic interest These effects have been defined in anesthetized animals but there is a paucity of data in man In the present study its effects on hemodynamics in 20 patients given 10 mg of the compound at the time of diagnostic cardiac catheterization have therefore been evaluated

Methods

Patients studied Twenty patients with cardiac disease were studied The nature of the investigation was explained to every patient and informed consent was obtained The design of the protocol was approved by the Ethics Committee of Green Lane Hospital

Clinically seven patients were Class III and 13 Class II (New York Heart Association functional classification) Twelve had coronary artery disease and eight had rheumatic valvular defects There were 13 males and seven females ranging in age from 20 to 62 years mean 46 years. The relevant clinical features and details of daily medication of all patients are summarized in Table I Patients who were on chronic propranolol therapy were studied 24 hours after the drug was discontinued Digoxin and furosemide were withheld for 12 hours preceding cardiac catheterization

Hemodynamic measurements Cardiac catheterization was performed through a right antecubital fossa cutdown an hour after premedication with 100 mg oral pentobarbitone At the end of the diagnostic procedure at least 20 minutes were allowed to elapse before baseline hemodynamic measurements were made These were taken at 5 minute intervals until all hemodynamic variables were stable Duplicate measurements were then recorded and the mean of these two sets of data served as control A 10 mg dose of verapamil was administered intravenously over

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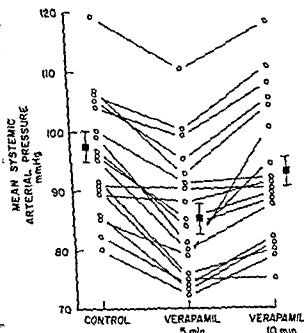


Fig 1 Change in mean arterial pressure following intravenous verapamil administration Individual values (open circles) for 18 patients are shown as well as the mean (closed squares) and standard errors of means (horizontal bars) There was a significant decrease in mean arterial pressure at 5 minutes (p < 0 01) after drug administration

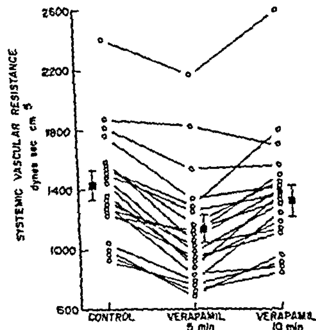


Fig 2 Effect of verapamil administration on systemic vascular resistance Individual values are shown by open circles and closed squares represent means with standard errors of means (horizontal bars) Five minutes after verapamil a significant decrease (p < 0 001) in vascular resistance occurred

Table II Hemodynamic effects of intravenous verapamil in patients with cardiac disease

Hemodynamic variables	*Control (mean ± SEM)*	*3 5 minutes after IV verapamil (mean ± SEM)*	*Significance of difference from control*	*10 minutes after IV verapamil (mean ± SEM)*	*Significance of difference from control*
Heart rate beats/min (n = 18)	75 " ± 3.0	80 2 ± 2.8	NS	.9 ± 2.9	NS
Aortic pressure mm Hg (n = 18)					
Systolic	131 0 ± 5.5	115 8 ± 4 7	p < 0 05	12. 9 ± 5 49	NS
Diastolic	9 8 ± 2.5	69 1 ± 2 8	p < 0 01	73 9 ± 2.8	NS
Mean	97 8 ± 3 4	85 9 ± 2.7	p < 0 01	92.9 ± 2.7	NS
Pulmonary artery pressure mm Hg (n = 19)					
Systolic	24 2 ± 1 3	?5 7 ± 1 0	NS	23.8 ± 1 0	NS
Diastolic	10 3 ± 0 7	11.9 ± 0 7	NS	10 7 ± 0 5	NS
Mean	15 7 ± 1 0	18 1 ± 0 8	NS	13 6 ± 0 8	NS
Left ventricular end-diastolic pressure mm Hg (n = 20)	11 0 ± 0 9	15 0 ± 1 0	p < 0 01	13.3 ± 1 0	NS
Cardiac index L/min /M (n = 20)	3 17 ± 0 15	3 61 ± 0 17	NS	3.30 ± 0 16	NS
Stroke volume index ml./beat/M (n = 20)	43 0 ± 2 4	46 0 ± 2 1	NS	45.3 ± 2 5	NS
Systemic vascular resistance dynes sec cm	1435 ± 80	1131 ± 8?	p < 0 001	1305 ± 87	NS
LV work index Kg m /min /M (n = 20)	3 63 ± 0 28	3 31 ± 0 23	NS	3 44 ± 0 ?4	NS
LV dp/dt max mm. Hg/sec (n = 11)	1343 ± 15?	1007 ± 10?	p < 0 0.	1216 ± 96	NS

Abbreviations n = numbe of patients NS = not statist lly significant SEM = standard error of mean

Table I Clinical data of patients given intravenous verapamil at diagnostic cardiac catheterization

Patient no./sex	Age	Diagnosis	EF (%)	BSA (M^2)	Functional Class (N.Y. Heart Association)	Concomitant therapy
1/F	21	RHD	53	1.62	II	Digoxin 0.25 mg b.i.d.
2/M	40	RHD	70	1.96	II	Digoxin 0.25 mg b.i.d.
3/M	57	CAD	71	1.70	II	Propranolol 40 mg q.i.d.
4/M	57	CAD	76	2.0	III	Propranolol 80 mg q.i.d.
5/M	55	CAD	72	2.0	II	Nitroglycerin PRN
6/M	48	CAD	61	1.90	II	Propranolol 40 mg q.i.d.
7/M	36	RHD	39	1.75	II	Furosemide 40 mg daily
8/M	23	RHD	55	1.52	III	Furosemide 40 mg daily
9/M	38	CAD	37	1.50	III	Propranolol, 40 mg q.i.d.
10/F	56	CAD	74	1.62	II	Propranolol 40 mg q.i.d.
11/M	20	RHD	69	1.70	III	Digoxin 0.25 mg b.i.d.
12/F	58	CAD	43	1.85	II	Nitroglycerin PRN
13/M	58	CAD	58	1.77	II	Propranolol 40 mg q.i.d.
14/M	62	CAD	67	1.90	II	Nitroglycerin PRN
15/M	53	CAD	53	1.91	II	Propranolol 40 mg q.i.d.
16/F	48	CAD	74	1.90	III	Propranolol 80 mg q.i.d.
17/F	32	RHD	62	1.72	III	Digoxin 0.25 mg b.i.d.
18/F	26	RHD	66	1.83	II	Furosemide 40 mg daily
19/M	54	CAD	46	1.88	II	Nitroglycerin PRN
20/M	58	CAD	44	1.91	III	Digoxin 0.25 mg daily Propranolol 40 mg q.i.d.

Abbreviations: M = male; F = female; EF = ejection fraction; BSA = body surface area; RHD = rheumatic heart disease; CAD = coronary artery disease.
The ejection fractions were computed from left ventricular volume measurements using single plane angiocardiograms.

2 minutes with a continuous monitoring of the electrocardiogram (generally Lead II) and phasic aortic pressure. All hemodynamic variables were measured between 3 and 5 minutes and again between 9 and 11 minutes following the completion of drug administration.

Pressures in the right and left sides of the heart were measured through 125 cm long No. 7 Cournand catheters, connected to Statham P23Db transducers, with zero pressure level set at the mid chest position. The pressure and electrocardiographic signals were displayed on Electronics for Medicine DR8 recorder with a photographic output. Mean pressures were obtained by electronic integration and the maximum first derivative of the left ventricular pressure (LVdp/dt max) was measured directly from the photographic records. Preliminary studies (unpublished) in our laboratory comparing the output from a Statham SFK1 high fidelity catheter tip manometers with conventional fluid filled catheter assembly showed that for absolute values of LVdp/dt max below 2000 mm Hg/sec, the discrepancy between the two catheter systems was less than 10 per cent.

Cardiac output was determined in duplicate by the indicator dilution method. 10 mg of indocyanine green in 1.0 ml diluent was injected into the main pulmonary artery followed immediately by a saline flush. Blood was sampled from the aorta by a Harvard constant infusion pump at a rate of 20 ml per minute through a Gilford densitometer. Cardiac output was computed from the indicator dilution curves using the Hamilton formula.

Systemic vascular resistance (SVR, dynes sec cm) was calculated as follows:

$$SVR = \frac{A_oM}{CO}$$

where A_oM = mean aortic pressure (mm Hg); CO = cardiac output (liters/min). Left ventricular work index (LVWI, Kg m/M^2) was calculated using the formula:

$$LVWI = (A_oM \times LVEDP) \times CI \times 1.36 \times 10^{-2}$$

where CI = cardiac index (liters/min/M^2), $LVEDP$ = left ventricular end diastolic pressure. Statistical analyses were performed using a paired Student's t test for significance of differ

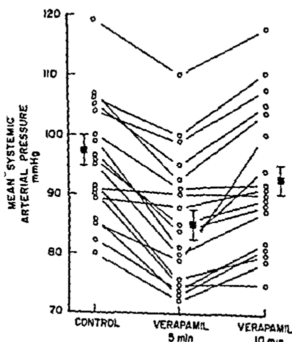


Fig. 1. Change in mean arterial pressure following intravenous verapamil administration. Individual values (*open circles*) for 18 patients are shown as well as the mean (*closed squares*) and standard errors of means (*horizontal bars*). There was a significant decrease in mean arterial pressure at 5 minutes ($p < 0.01$) after drug administration.

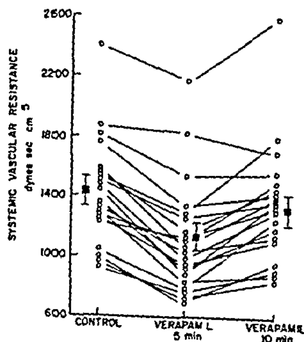


Fig. 2. Effect of verapamil administration on systemic vascular resistance. Individual values are shown by *open circles* and *closed squares* represent means with standard errors of means (*horizontal bars*). Five minutes after verapamil a significant decrease ($p < 0.001$) in vascular resistance occurred.

Table II. Hemodynamic effects of intravenous verapamil in patients with cardiac disease

Hemodynamic variables	*Control (mean ± SEM)*	*3-5 minutes after IV verapamil (mean ± SEM)*	*Significance of difference from control*	*10 minutes after IV verapamil (mean ± SEM)*	*Significance of difference from control*
Heart rate beats/min. (n = 18)	75.[illegible] ± 3.0	80.[illegible] ± 2.8	NS	[illegible]5.9 ± 2.9	NS
Aortic pressure mm. Hg (n = 18)					
Systolic	131.0 ± 5.5	115.8 ± 4.[illegible]	p < 0.05	125.9 ± 5.49	NS
Diastolic	98 ± 2.5	69.1 ± 2.8	p < 0.01	[illegible]3.9 ± 2.8	NS
Mean	9[illegible].8 ± 3.4	8[illegible].9 ± 2.7	p < 0.01	92.9 ± 2.7	NS
Pulmonary artery pressure mm Hg (n = 19)					
Systolic	[illegible]4.2 ± 1.3	25.7 ± 1.0	NS	23.8 ± 1.0	NS
Diastolic	10.3 ± 0.7	11.9 ± 0.7	NS	10.7 ± 0.5	NS
Mean	15.7 ± 1.0	18.1 ± 0.8	NS	15.6 ± 0.8	NS
Left ventricular end-diastolic pressure mm Hg (n = 20)	11.0 ± 0.9	15.0 ± 1.0	p < 0.01	13.3 ± 1.0	NS
Cardiac index L./min./M. (n = 20)	3.17 ± 0.15	3.61 ± 0.17	NS	3.30 ± 0.16	NS
Stroke volume index ml./beat/M. (n = 20)	43.0 ± 2.4	46.0 ± 2.1	NS	45.3 ± 2.5	NS
Systemic vascular resistance dynes sec cm	1435 ± 80	1131 ± 8[illegible]	p < 0.001	130[illegible] ± 87	NS
LV work index Kg m/min/M (n = 20)	3.63 ± 0.28	3.31 ± 0.23	NS	3.44 ± 0.[illegible]4	NS
LV dp/dt max mm Hg/sec (n = 11)	1343 ± 152	1007 ± 10[illegible]	p < 0.05	1216 ± 96	NS

Abbreviations: n = number of patients; NS = not statistically significant; SEM = standard error of mean.

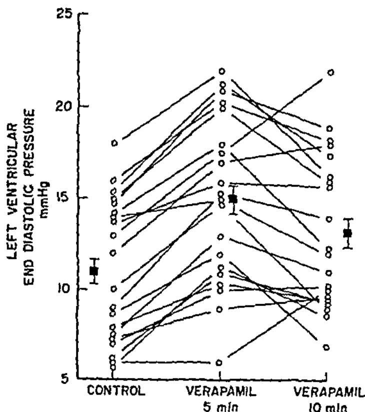


Fig 3 Changes in left ventricular end diastolic pressure following verapamil administration Details as in *Fig 2* A significant increase ($p < 0.01$) in the left ventricular filling pressure occurred

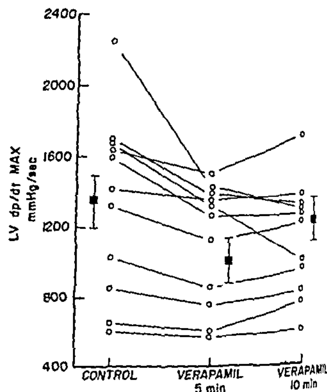


Fig 4 Left ventricular dp/dt max before and after intravenous verapamil in 11 patients Details as in Fig 2 Note the mean decrease at 5 minutes ($p < 0.05$)

ences between control data and those after the administration of verapamil

Results

The hemodynamic effects following intravenous verapamil in 20 patients with heart disease are summarized in Table II The changes which were maximal between 3 and 5 minutes after drug injection were transient and by 10 minutes the differences between the control values and those after verapamil were no longer statistically significant

Verapamil produced a fall in systolic (−12 per cent $p < 0.05$), diastolic (−14 per cent $p < 0.01$) and mean (−12 per cent $p < 0.01$ Fig 1) aortic pressures accompanied by a significant fall (−21 per cent $p < 0.001$ Fig 2) in systemic vascular resistance There was, however no significant effect on pulmonary artery pressures Pulmonary capillary wedge pressures were not measured Verapamil had a variable effect on heart rate cardiac index and stroke volume index, producing minor increases in the mean values for these parameters for most patients but the changes did not reach statistical significance

Verapamil produced a 36 per cent increase in LVEDP The response was similar in 11 patients whose resting LVEDP was below 12 mm Hg as well as in nine patients whose LVEDP ranged between 11 and 18 mm Hg (Fig 3) In only one patient with baseline level of 6 mm Hg was there no increase in LVEDP at 5 minutes after verapamil administration an increase to 10 mm Hg however occurred at 10 minutes

In 11 patients LVdp/dt max was measured before and at 5 minutes as well as at 10 minutes after verapamil administration The results are presented in Fig 4 During the peak effect of the drug there was a 25 per cent ($p < 0.05$) reduction in LVdp/dt max Records from a patient demonstrating a typical response of LVdp/dt max obtained by electronically differentiating a high fidelity record of left ventricular pressure trace are shown in Fig 5 In this patient the reduction in the first derivative (by 10 per cent) was accompanied by an increase in LVEDP with a fall in the peak systolic left ventricular pressure

The effects of intravenous verapamil on the electrocardiogram (Lead II) were examined in all 20 patients Two patients developed junctional rhythm about 3 minutes after verapamil was given with a gradual return to sinus rhythm after

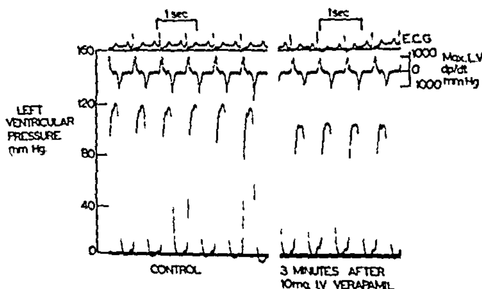


Fig 5 Effects of verapamil on left ventricular contractility in a patient with coronary artery disease The left ventricular pressure was increased by high fidelity catheter tip manometry during cardiac catheterization and the first derivative of the pressure (LVdp/dt max) was obtained by electronic differentiation Verapamil diminished the peak systolic left ventricular pressure and raised the left ventricular end-diastolic pressure it produced only a small decrease in LVdp/dt There was no change in heart rate

10 minutes The mean results for the remaining 18 patients analyzed for significance by Student's t test for paired data are presented in Table III The peak effects of the compound usually apparent between 5 and 10 minutes after its administration have been compared with the baseline values In two patients the Q T intervals could not be measured accurately because of low amplitude of the T waves They were therefore excluded from the mean values (n = 16) shown in Table III No significant changes were found with respect to the R R QRS and Q T_c intervals The P R interval however increased after verapamil in all patients The mean change (+14 per cent) from 182.4 ± 5.6 msec to 207.2 ± 8.4 msec was highly significant ($p < 0.001$)

Discussion

Intravenous verapamil in the present study in patients with ischemic and rheumatic heart disease in sinus rhythm was found to produce significant decreases in systemic vascular resistance and LVdp/dt max which was used as an index of contractility These changes were accompanied by a comparable rise in LVEDP but with only trivial and statistically insignificant increases in forward stroke volume cardiac index

Table III Effects of intravenous verapamil on the electrocardiogram in patients with sinus rhythm

Interval (in msec)	*Baseline*	*Five minutes after IV verapamil*	*n*	*Significance of difference from baseline*
R R	[illegible] ± 41	751 ± 30	18	S
P R	182.4 ± 5.6	207.2 ± 8.4	18	p < 0.001
QRS	63.5 ± 4.4	[illegible] ± 4.1	18	NS
Q T	[illegible] ± 9.3	[illegible] ± [illegible]	16	NS

n = number of patients NS = not statistically significant

and heart rate The over all hemodynamic changes were transient in most patients This short lived effect of the drug is consistent with the observation in animals that after single intravenous injections of the drug no trace of free verapamil would be found in the plasma ten minutes later The changes in pulmonary artery pressures were minor the pulmonary artery diastolic pressure rose after verapamil but not significantly The net effects of the drug in a dose previously demonstrated to be effective in the treatment of supraventricular tachyarrhythmias are thus similar to those of amiodarone [7] resulting from a complex interplay of simultaneous alterations in preload afterload myocardial contractility and in all probability coronary

blood flow, since verapamil and amiodarone are both potent coronary vasodilators[17, 18] However, the effects of verapamil on coronary blood flow were not evaluated in the present series of patients

The hemodynamic effects of verapamil are, therefore in contrast to those of conventional afterload reducing agents, nitroprusside, phentolamine or nitroglycerin all of which may produce a significant increase in forward stroke volume in association with a decrease in left ventricular filling pressure[19] Our findings suggest that verapamil also reduces afterload as judged by a significant reduction in systemic arterial pressure and systemic vascular resistance However in the case of verapamil the expected increases in forward stroke volume resulting from the observed decreases in systemic arterial pressure and vascular resistance appeared to be offset almost completely by the concomitant reduction in contractility as indicated by reduced LVdp/dt max with an increase in LVEDP Despite the depressant effect on contractility a reduction in cardiac index did not occur even in patients with raised LVEDP and abnormally low ejection fractions However, none of the patients in the present series was in Functional Class IV and all had basal LVEDPs below 20 mm Hg with ejection fractions exceeding 40 per cent It is thus possible that a reduction in cardiac index might occur in patients with lower ejection fractions or when larger doses of the drug are administered A dose dependent reduction in cardiac output and stroke volume has been shown to occur with verapamil in experimental animals For example in anesthetized dogs Ross and Jorgensen[11] found that the hypotensive effect of verapamil could be wholly accounted for by peripheral vasodilation in intravenous doses below 0 25 mg /Kg body weight Larger doses reduced cardiac output and stroke volume consistent with the known propensity of the drug to reduce contractility and to interfere with excitation-contraction coupling in cardiac muscle[10]

Although our studies were undertaken in patients with normal rhythm differences in the hemodynamic effects of verapamil in patients in sinus rhythm and in those with chronic atrial fibrillation have been emphasized by Ryden and Saetre[20] Their preliminary studies involving right heart catheterization in subjects in sinus rhythm are similar to those here Of particular interest was their finding of a small but a significant increase in heart rate after verapamil due undoubtedly to a reflex response to hypotension Such a reflex tachycardia was also apparent in our own patients In contrast, in anesthetized animals verapamil usually produces bradycardia[11] which may be related to a non competitive inhibition of sympathetic excitation[13] Verapamil also has a depressant effect on nodal tissues and latent pacemakers by inhibiting calcium mediated slow response[1, 13] This effect may summate with that of beta adrenergic blocking drugs[10] and potentially lethal ventricular asystole and hypotension may result as a consequence of this combination therapy,[1] especially in patients with severe cardiac decompensation In our own patients, propranolol was discontinued at least 24 hours before the effects of verapamil were evaluated and an unexpected fall in blood pressure was not encountered

The fact that verapamil does not affect the rate of depolarization or repolarization of the action potential[1] is consistent with our observations that the drug had no effect on the QRS or QT intervals of the electrocardiogram The prolongation of the P R interval found in our studies as well as in those of others[9] is also in line with the known depressant action of the drug on A V conduction confirmed by His bundle electrocardiography[23] The retardation of the anterograde A V conduction by verapamil undoubtedly accounts for the beneficial action of the drug on supraventricular tachycardia due to nodal re entry[1] However in the case of atrial fibrillation the effect on A V conduction may result in a slow ventricular response with a reduction in cardiac output[9]

From the standpoint of advances in therapy we have previously shown that verapamil produces a prompt and predictable reversion of about 80 per cent of cases of paroxysmal supraventricular tachycardias to sinus rhythm[6] This is likely to become the main indication for the use of the drug in cardiovascular therapeutics Our present studies have shown that the intravenous dose required for this antiarrhythmic action does not produce severe depression of hemodynamic variables in patients with cardiac disease the effects on systemic arterial pressure, systemic vascular resistance left ventricular filling pressure, and contractility being mild to moderate in severity and relatively short lived Caution

should nevertheless be exercised in the use of verapamil in patients with severe myocardial decompensation especially in combination with beta adrenergic blocking drugs since the depressant actions of these compounds are likely to be additive in this context and prove deleterious

Summary

The hemodynamic effects of intravenous verapamil (10 mg) were evaluated in 13 patients with coronary artery disease and in seven patients with rheumatic valvular disease during cardiac catheterization The peak effects were apparent at 3 to 5 minutes after injection and lasted about 10 minutes The mean arterial pressure fell from 97.8 ± 3.4 to 85.9 ± 2.7 mm Hg (−12 per cent $p < 0.01$) accompanied by a significant decrease (−21 per cent $p < 0.001$) in systemic vascular resistance (from 1435 ± 80 to 1131 ± 82 dynes sec cm⁻⁵) with an increase in left ventricular end-diastolic pressure (from 11.0 ± 0.9 to 15.0 ± 1.0 mm Hg +36 per cent $p < 0.01$) and a reduction in LV dp/dt max (from 1343 ± 152 to 1007 ± 102 mm Hg/sec −25 per cent $p < 0.05$) The changes in heart rate (from 75.7 ± 3.0 to 80.2 ± 2.8 beats/min) cardiac index (from 3.17 ± 0.15 to 3.61 ± 0.17 L/min/M²) left ventricular minute work (from 3.63 ± 0.28 to 3.31 ± 0.23 kg m/min/M²) and mean pulmonary artery pressures (from 15.7 ± 1.0 to 18.1 ± 0.8 mm Hg) were not statistically significant The intrinsic negative inotropic action of verapamil is therefore minimized by its effect on afterload so that cardiac index is not reduced by the drug in patients with cardiac disease

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Effect of magnesium chloride on electrical stability of the heart

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Previous reports have indicated the relationship between hypomagnesemia and cardiac arrhythmias[1] Consequently correction of magnesium deficiency has been found to restore normal cardiac rhythm and no beneficial effects have been expected in the absence of hypomagnesemia Our recent studies have demonstrated the usefulness of magnesium in control of serious digitalis toxic arrhythmias in the presence of normal magnesium levels The mode of this beneficial action however has remained speculative[2] Therefore the present investigation was undertaken to examine the effect of magnesium on the threshold of ventricular fibrillation and the threshold of ventricular premature contractions in normal and digitalis treated dogs

Materials and methods

Twenty adult mongrel dogs weighing 16 ± 4 3 kilograms were divided into three groups (a) intact control dogs (b) intact digitalized dogs and (c) Starling heart-lung preparations The animals were anesthetized with 25 to 30 mg per kilogram sodium pentobarbital and artificial respiration was maintained on room air via an endotracheal tube Seven of the intact dogs were treated with digoxin (0 05 mg per kilogram) given intravenously approximately 24 hours before the studies A bipolar stimulation catheter was introduced through a peripheral vein and was positioned at the right ventricular apex under fluoroscopic control Lead II electrocardiogram and arterial blood pressure were monitored continuously The inflow and outflow resistance and thus the venous return the blood pressure and the cardiac output were kept constant in the heart-lung preparations The electrical stimuli were delivered by means of a Grass stimulator connected to the electrode catheter A 20 per cent solution of magnesium chloride in distilled water was prepared for parenteral use

The ventricular premature contraction threshold (VPCT) and the ventricular fibrillation threshold (VFT) were determined as follows electrical stimulation was initiated below 0 1 mV through the endocardial bipolar catheter at a frequency of 1 200/second which was kept constant throughout the experiments The electrical stimuli were delivered throughout the cardiac cycle and therefore, the entire ST segment and T wave The voltage was gradually increased until a ventricular premature contraction was elicited and further increments were continued to the point of ventricular fibrillation VPCT and VFT were defined as the minimal voltage required to induce a ventricular premature contraction and ventricular fibrillation respectively Ventricular defibrillation was accomplished by direct current countershock within 20 to 30 seconds after fibrillation These observations were made at 15 minute intervals in order to allow time for recovery After the ascertainment of control values of VPCT and VFT magnesium chloride solution was bolus injected intravenously in the dosage of 100 mg /kg Fifteen minutes afterwards when the heart rate and blood pressure were similar to the stable control state the values of VPCT and VFT were determined again in the same fashion as d earlier

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Table I. Values of ventricular premature contraction threshold (VPCT) and ventricular fibrillation threshold (VFT) given in millivolt (mean ± S.E.M.) before and after treatment with magnesium chloride

Group	Number of dogs	VPCT control	VPCT after magnesium	t value	VFT control	VFT after magnesium	t value
A Intact control dogs	9	0.19 ± 0.01	0.29 ± 0.03	< 0.01	0.50 ± 0.06	1.54 ± 0.70	< 0.01
B Intact digitalized dogs	7	0.18 ± 0.01	0.35 ± 0.04	< 0.0[illegible]	0.47 ± 0.09	0.89 ± 0.08*	< 0.05
C Heart-lung preparations	4	0.29 ± 0.06	0.50 ± 0.09	< 0.01	0.49 ± 0.10	1.13 ± 0.[illegible]	< 0.05

*These values are only in four dogs. See text for details.

The data obtained from these studies were analyzed by Student's t test and the results are summarized in Table I.

Results

Effect of magnesium on intact control dogs. The threshold of ventricular premature contractions in Group A was 0.19 ± 0.01 mV, which increased by 53 per cent after administration of magnesium ($P < 0.01$). The VFT in this group was 0.50 ± 0.06 mV, which increased to 1.54 ± 0.70 mV following magnesium treatment. Ventricular defibrillation was easily achieved in all of the nine dogs of this group with 150 W./sec.

Effect of magnesium on digitalis-treated dogs. In Group B, the control threshold of ventricular premature contraction was 0.18 ± 0.01 mV. After administration of magnesium chloride, this value increased to 0.35 ± 0.04 mV. The VFT in this group measured 0.47 ± 0.09 mV. However, ventricular defibrillation proved to be difficult in these animals after the initial ventricular fibrillation (prior to administration of magnesium chloride). Three of the seven dogs could not be defibrillated with repeated 400 W./sec. countershocks, resulting in death. Three of the four surviving animals exhibited spontaneous ventricular premature contractions which were abolished after administration of magnesium. VFT in the four surviving animals increased to 0.89 ± 0.08 mV following magnesium treatment.

Effect of magnesium on heart-lung preparations. The control value of VPCT was 0.29 ± 0.06 mV, which increased by 72 per cent after magnesium treatment ($P < 0.01$). Likewise, an elevation of VFT by 131 per cent was effected by magnesium (Table I). Internal defibrillation was easily achieved with 50 W./sec. in this group.

Discussion

These studies demonstrate that magnesium reduced the vulnerability of the heart to life-endangering ventricular arrhythmias. Investigations from our laboratories have shown that magnesium can effectively restore normal sinus rhythm in dogs with digitalis-induced ventricular tachyarrhythmias. The antiarrhythmic effectiveness of magnesium did not appear to be due to hemodynamic alterations or changes in the serum electrolytes or digoxin levels. The autonomic actions of magnesium, however, may be considered to influence the threshold of arrhythmias.[5] Changes in the autonomic tone do not seem to be the dominant factor, as the denervated hearts (heart-lung preparations) in the present study also gained the higher ventricular threshold of arrhythmias after magnesium administration similar to that achieved by the intact dogs. The mechanism of antiarrhythmic action of magnesium has been explored by other investigators and it does not appear to be related to reactivation of digoxin-inhibited (Na-K) ATPase, alteration in digoxin binding, or due to autonomic influences. A modulation of the transmembrane ionic fluxes at the cellular level still remains possible and deserves further investigation.

The results of these experiments indicate that magnesium elevates the ventricular threshold of premature contraction and fibrillation in the normal, digitalized, and denervated heart of the dog and therefore may be valuable in the management of serious ventricular arrhythmias.

Summary

The effect of magnesium chloride on the ventricular fibrillation threshold (VFT) and the threshold for the ventricular premature contraction (VPCT) was studied in 20 dogs. Seven of the dogs were pre treated with digitalis and four were in the form of heart-lung preparations. In the anesthetized, intact dogs, the VPCT was 0.19 ± 0.01 mV. After treatment with magnesium chloride (100 mg per kilogram intravenously) the VPCT increased by 53 per cent ($P < 0.01$). In the same group of animals, the VFT averaged 0.50 ± 0.06 mV, which more than doubled after administration of magnesium. The threshold of VPC in the digitalis treated dogs measured 0.18 ± 0.01 mV; this value doubled after magnesium. The VFT in the digitalized dogs also increased after magnesium; however resistance to electrical defibrillation was encountered in this group. In the heart-lung preparations, VPCT improved by 72 per cent and a gain of 131 per cent in the VFT followed magnesium administration.

The results suggest that magnesium increases the ventricular threshold of arrhythmias in normal, denervated (heart-lung preparations) and also digitalis treated hearts and, thus, indicate its usefulness in the treatment of ventricular arrhythmias.

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The role of local disparity in conduction and recovery time on ventricular vulnerability to fibrillation

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It is well known that changes and conduction time refractory period and recovery time of conducted beats in the ventricle all have influence on ventricular vulnerability to fibrillation as do local differences in excitability The latter first pointed out by Garrey in 1914 has since been emphasized by many investigators and in recent years by Moe and Han and associates [1-7] However the interrelationship of these electrophysiological parameters and their role with respect to ventricular vulnerability to fibrillation needs further evaluation Therefore the purpose of this investigation was to measure each of these parameters together with ventricular fibrillation threshold in dogs under various experimental conditions

Methods

Experiments were performed on mongrel dogs ranging in weight from 20 to 35 kilograms and anesthetized by an intravenous injection of sodium pentobarbital in a dose of 35 mg per kilogram of body weight Under artificial respiration the chest was opened in the midline and the heart was cradled in the opened pericardium The sinoatrial node was inactivated by crushing and the heart was paced at a constant rate by electrical stimuli applied to the ventricle

After 5 000 to 8 000 units of Heparin was given intravenously a shunt between the left carotid artery and the anterior descending branch of the left coronary artery was established by cannulating the carotid artery with a polyethylene catheter having an internal diameter of 0 07 inch and connecting it to another polyethylene catheter inserted into a free part of the anterior descending branch of the left coronary artery (Fig 1) The latter catheter depending on the size of the coronary artery had an internal diameter of 0 034 or 0 055 inch During the cannulation of the coronary artery care was taken not to occlude any side branches A side branch free distance of 6 to 8 mm was usually sufficient to achieve this goal By an injection of Evans blue into the shunt the area perfused by the cannulated artery could be readily defined in the left ventricle

Bipolar stimulating electrodes consisting of a pair of small stainless steel hooks were applied to the left ventricle within the perfused area (S_1) to the right ventricle in the nonperfused area (S_2) approximately 30 mm from the edge of the perfused area and over the septum on the boundary (S_3) between the perfused and non perfused areas For the application of basic pacing stimuli another pair of stimulating electrodes (S_4) was attached to the right ventricle near the origin of the pulmonary artery Unipolar recording electrodes were also located at a distance of 25 to 30 mm from the stimulating electrode S_1 in the perfused area (R_1) and at the same distance from the stimulating electrode S_2 in the non perfused area (R_2) A needle inserted subcutaneously in the right hind leg served as the indifferent electrode for the unipolar recording system

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Summary

The effect of magnesium chloride on the ventricular fibrillation threshold (VFT) and the threshold for the ventricular premature contraction (VPCT) was studied in 20 dogs Seven of the dogs were pre treated with digitalis and four were in the form of heart-lung preparations In the anesthetized, intact dogs, the VPCT was 0 19 ± 0 01 mV After treatment with magnesium chloride (100 mg per kilogram intravenously) the VPCT increased by 53 per cent ($P < 0 01$) In the same group of animals, the VFT averaged 0 50 ± 0 06 mV, which more than doubled after administration of magnesium The threshold of VPC in the digitalis treated dogs measured 0 18 ± 0 01 mV this value doubled after magnesium The VFT in the digitalized dogs also increased after magnesium, however, resistance to electrical defibrillation was encountered in this group In the heart-lung preparations, VPCT improved by 72 per cent and a gain of 131 per cent in the VFT followed magnesium administration The results suggest that magnesium increases the ventricular threshold of arrhythmias in normal denervated (heart-lung preparations) and also digitalis treated hearts and, thus, indicate its usefulness in the treatment of ventricular arrhythmias

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ments and samples taken 5 to 10 minutes after the beginning of local K infusion The mean values were 4 2 mEq/L in the control and 4 3 mEq/L during local K infusion A marked ST segment elevation in the unipolar electrogram over the perfused area indicated locally induced hyperkalemia as has been previously described Ventricular ectopic activity was common during the initial 5 minutes of local K infusion However the ectopic activity decreased thereafter so that during the following 10 minutes the experimental measurements were usually made under stable pacing conditions No enhanced ectopic activity was observed in experiments with systemic K infusion During systemic K infusion the serum K concentration increased steadily and attained a constant mean level of 9 4 mEq/L about 20 minutes after the beginning of infusion

With local infusion of epinephrine the mean systolic blood pressure increased during the first minute by 5 to 8 mm Hg probably due to a positive inotropic effect on the perfused part of the left ventricle The same amount of epinephrine given intravenously resulted in no change in the blood pressure Similar to the local K infusion ventricular ectopic activity was markedly increased during the first several minutes of local epinephrine infusion and generally decreased about 5 minutes after the start of infusion In contrast to the effect of systemic K infusion systemic epinephrine infusion led initially to some ventricular ectopic activity and to accelerated atrioventricular nodal rhythm which sometimes competed with ventricular pacing at a cycle length of 400 msec However ventricular ectopic beats usually subsided and the nodal rate decreased sufficiently to achieve stable pacing conditions about 30 minutes after the start of infusion The systolic blood pressure increased during the first several minutes of systemic epinephrine infusion by 60 to 75 mm Hg fell subsequently and stabilized at approximately 50 mm Hg above the control level about 15 minutes after the beginning of infusion

1 Fibrillation threshold VFTs were found to be lower during local infusions of K or epinephrine and higher during systemic infusions of K or epinephrine than in the control values (Fig 2) In the series of K infusions the mean VFT was 16 mA in the control state and it decreased to 8 8 mA during local infusion and increased to 31 9

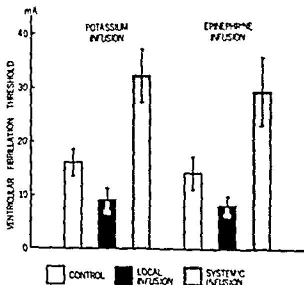


Fig 2 Comparison of VFTs obtained in the control state and during local and systemic infusions of potassium or epinephrine The values are expressed as mean ± SE

mA during systemic infusion ($P < 0.03$) In the series of epinephrine infusions the mean VFT was 14 mA in the control and it decreased to 7 6 mA during local infusion and increased to 22 9 mA during systemic infusion ($P < 0.03$) Fig 3 depicts two typical experiments showing the decreased VFT during local infusion and the increased VFT during systemic infusion of K or epinephrine In the top panel VFT was 6 mA in the control and it decreased to 4 mA during local infusion and increased to 10 mA during systemic infusion of K In the bottom panel VFT was 5 mA in the control and it decreased to 4 mA during local infusion and increased to 12 mA during systemic infusion of epinephrine

2 Conduction time As shown in Table I the mean CT over the perfused area was 46 msec in the control and increased to 52 msec during local infusion and to 51 during systemic infusion of K ($P < 0.03$) The mean CT over the non perfused area was 25 msec in the control and it did not change significantly during local and systemic K infusions The mean CT over the perfused area was 40 msec in the control and it decreased slightly to 36 msec during local infusion and to 38 msec during systemic infusion of epinephrine ($P < 0.05$) The mean CT over the non perfused area was 27 msec in the control and it did not change significantly during local and systemic epinephrine infusions The significant difference in CTs was noted between the perfused and non

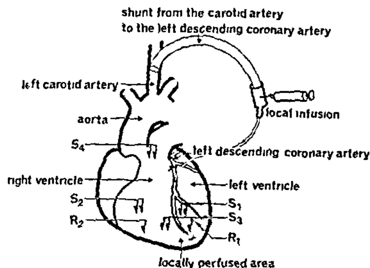


Fig 1 Diagram of experimental design S = stimulating electrodes R = recording electrodes See text for detailed description

*The following measurements were then com*pleted in each experiment

1 Local refractory periods (RP) were mea*sured in the perfused and non perfused areas by* pacing the ventricle by delivering basic stimuli through S_1 or S and applying premature stimuli S_1 or S *through the same electrode The inten*sity of basic and premature stimuli was twice the diastolic threshold in mA The premature interval S_1S_1 *or* S_2S *was gradually increased until the* earliest possible propagated response could be evoked by S_1 or S_2 The local RP was then *measured as the* S_1S_1' *or* S_2S_2 *interval at which* the earliest response was obtained

2 For the measurement of conduction time (CT) *within the perfused and non perfused areas* the intervals between the artifact of basic pacing stimuli applied to S_1 or S_2 and their propagated *responses at the recording electrodes* R_1 or R_2 were obtained

3 For the measurement of the recovery time *(RT) of conducted beats the ventricle was paced* through the stimulating electrodes S_4 at the base of the right ventricle Following a propagated impulse from S_4 premature stimuli of twice the diastolic threshold were applied in the perfused area (S_1) or in the non perfused area (S_2) to evoke the earliest possible response The local RT was then measured as the S_4S_1' or S S ' interval at which *the earliest response was obtained*

4 For the measurement of ventricular vulnerability to fibrillation the ventricle was paced *through the stimulating electrodes* S_3 and a train of rapid rectangular pulses was applied across the vulnerable period *after every twelfth basic* ventricular response The rapid pulses occurred at an interval of 10 msec (100 per second) and their *intensity was gradually increased until fibrilla*tion resulted Ventricular fibrillation threshold (VFT) was then defined as the minimum current *in mA which induced fibrillation*

The patterns of pacing and test stimuli delivered to the ventricle were programmed using a variable *interval* generator and a series of Tektronix waveform and pulse generators The output of the pulse generator triggered a Grass *stimulator which delivered pulses of 3 msec* duration to the ventricular stimulating electrodes The diastolic threshold was first deter*mined and the current of twice the threshold* value was used for all pacing and test stimuli except for measurements of VFT For registration *of all measurements a Lead III electrocardio*gram, unipolar local electrograms from the perfused and non perfused areas and the stimulus *artifacts were all recorded on an Electronics for* Medicine recorder with a paper speed of 100 mm / sec The stimuli were also displayed on an oscil*loscope and were calibrated by means of a* Tektronix current probe amplifier

In the first series of experiments using eight *dogs, measurements of RP CT, and RT in the* perfused and non perfused areas as well as measurements of VFT were taken in each dog in *the following manner (a) in the control state (b)* 5 minutes after the start of local infusion of isotonic KCl solution into the shunt *to the left anterior descending coronary artery at a rate of 2* to 6 mg /min and (c) 30 to 40 minutes after the start of systemic intravenous infusion of KCl at a rate of 20 to 40 mg /min Serum K levels were measured in the control state during local K infusion and during systemic K infusion *In the* second series again using eight dogs the same measurements as described above were taken in *the following manner (a) in the control state (b)* 5 minutes after the start of local infusion of epinephrine at a rate of 4 to 8 μg/min through the shunt and *(c) 30 to 40 minutes after the start of* systemic intravenous epinephrine infusion at a *rate of 40 to 80* μ*g/min*

Results

In all experiments *with local K infusion no* significant changes were observed in the serum K concentration between the control measure

Table I Changes in CT RP and RT in perfused and non perfused areas during potassium and epinephrine infusions

Potassium infusion mean values of 8 experiments

	Perfused area								*Non perfused area*					
	CT (msec)		*RP (msec)*		*RT (msec)*		*VFT (mA)*		*CT (msec)*		*RP (msec)*		*RT (msec)*	
	x	*SD*	*x̄*	*SD*	*x*	*SD*	*x*	*SD*	*x*	*SD*	*x̄*	*SD*	*x*	*SD*
Control	46	9.1	195	13.9	[illegible]	23.1	16.0	7.4	[illegible]	8.6	[illegible]	13.9	242	[illegible]
Local infusion	52	[illegible]	211	[illegible]	[illegible]	45.6	8.8	6.2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	14.1
Systemic infusion	51	11.5	214	15.9	[illegible]	41.8	31.9	[illegible]	[illegible]	11.3	[illegible]	[illegible]	280	[illegible]

Epinephrine infusion mean values of 8 experiments

	Perfused area								*Non perfused area*					
	CT (msec)		*RP (msec)*		*RT (msec)*		*VFT (mA)*		*CT (msec)*		*RP (msec)*		*RT (msec)*	
	x	*SD*	*x*	*SD*	*x*	*SD*	*x*	*SD*	*x*	*SD*	*x*	*SD*	*x*	*SD*
Control	40	15.4	183	[illegible]	[illegible]	[illegible]	14.0	8.6	[illegible]	[illegible]	[illegible]	21.0	[illegible]	[illegible]
Local infusion	36	17.3	156	11.5	224	15.8	[illegible]	4	[illegible]	4.3	[illegible]	19.6	[illegible]	21.0
Systemic infusion	38	[illegible]	163	8.1	231	13.4	[illegible]	[illegible]	[illegible]	4.2	[illegible]	9.4	[illegible]	[illegible]

CT = conduction time RP = refractory period RT = recovery time VFT = ventricular fibrillation threshold x = mean SD = standard deviation

of the perfused area was 183 msec in the control and it decreased to 156 msec during local infusion and to 163 msec during systemic infusion of epinephrine ($P < 0.03$) The mean RP of the non perfused area was 178 msec in the control and it did not change significantly during local perfusion but decreased to 15? msec during systemic infusion of epinephrine ($P < 0.03$) Again low VFT's were associated with localized prolongation or shortening of the mean RP during local perfusion of K or epinephrine

4 Recovery time The mean RT's were shorter in the non perfused area over the right ventricle than in the perfused area over the left ventricle due to the application of the pacing stimuli to the base of the right ventricle and shorter CT's through the right ventricular myocardium As shown in Table I the mean RT in the perfused area was 276 msec in the control and it increased to 302 msec during local and systemic infusions of K ($P < 0.03$) The mean RT in the non perfused area was 242 msec in the control and it did not change significantly during local infusion but increased to 280 msec during systemic infusion of K ($P < 0.03$) The mean RT in the perfused area was 2?6 msec in the control and it decreased to 224 msec during local infusion and to 231 msec during systemic infusion of epinephrine ($P < 0.03$) The mean RT in the non perfused area was 22? msec in the control and it did not change significantly during local infusion but decreased to 199 msec during systemic infusion of epinephrine ($P < 0.03$) Once again decreased VFT's were found to be associated with localized prolongation or shortening of the mean RT during local infusion of K or epinephrine

5 Local dispersion and VFT Fig 4 shows graphically the observed increases in CT RP and RT in the perfused and non perfused areas during local and systemic infusions of K It is apparent that during local infusion (L) the increases in the non perfused areas (ΔN) were small and those in the perfused areas (ΔP) were more pronounced During systemic infusion (S) the increases were apparent in the perfused areas (ΔP) as well as in the non perfused areas (ΔN) The absolute differences between ΔP and ΔN (ΔP − ΔN) indicate the degree of local disparity of CT RP and RT and they were generally greater during local infusion (ΔP − ΔN/l) than during systemic infusion (ΔP − ΔN/s)

Fig 5 shows that the similar findings were observed during local and systemic infusion of epinephrine The CT RP and RT all decreased in the experiments with epinephrine infusions It is obvious that the induced local dispersion of the electrophysiologic parameters was greater when marked decreases occurred in one area while no or

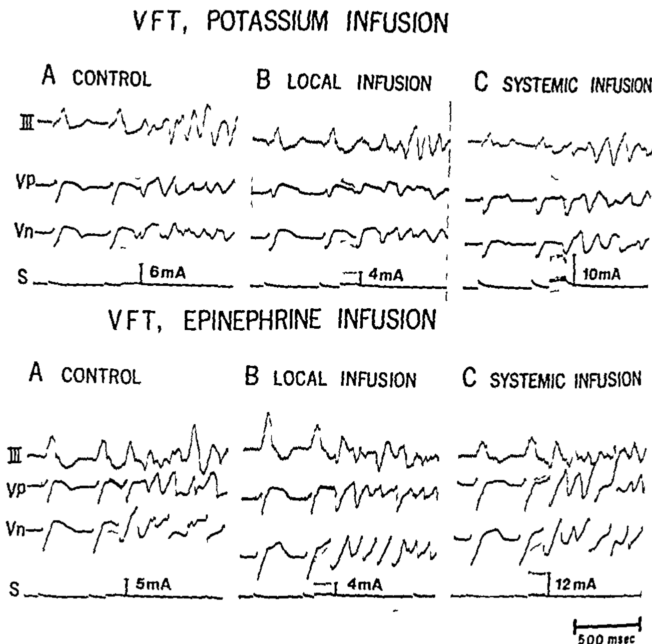


Fig 3 Measurements of VFT's in an experiment with potassium infusion on the *top panel* and in an experiment with epinephrine infusion on the *bottom* *III* = Lead III electrocardiogram *Vp* = ventricular local electrogram from the perfused area and *Vn* = from the non perfused area *S* = the artifact of stimuli applied to the stimulating electrodes See text for description

perfused areas in spite of the identical distances This was probably due to the relative thickness of the left ventricular myocardium over which the perfused area was chosen Since the impulse over the left ventricle has to traverse a thicker layer of the slowly conducting myocardium before it reaches the faster conducting Purkinje system the impulse propagation requires more time to travel in the left ventricle than in the right ventricle VFT's decreased (or ventricular vulnerability to fibrillation increased) significantly during local infusion of K or epinephrine This occurred whether the mean CT was increased by K or reduced by epinephrine in the perfused area indicating the important role of increased nonuniformity of conduction in the ventricles during local perfusion of these two agents

3 **Refractory period** As shown in Table I, the mean RP of the perfused area was 195 msec in the control and it increased to 211 msec during local infusion and to 214 msec during systemic infusion of K ($P < 0.03$) The mean RP of the non perfused area was 192 msec in the control and it did not change significantly during local infusion but increased to 208 msec during systemic infusion of K ($P < 0.03$) The mean RP

observed a significant decrease in ventricular fibrillation threshold during localized myocardial hyperkalemia It has been observed that systemic epinephrine infusion leads to an increase in ventricular vulnerability to fibrillation at the start of infusion This is presumably due to an uneven distribution of epinephrine within the myocardium[11] A marked increase in the ventricular vulnerability was to be expected in the present study during local epinephrine infusions because greater local differences in epinephrine concentrations were present and were maintained in the ventricular myocardium

The observation that local infusion of a substance can increase the ventricular vulnerability while the same substance given intravenously does not increase it indicates strongly the importance of local differences in distribution of the substance for the ventricular vulnerability This could be achieved in one experimental series with a drug which decreases CT RP and RT and in another series with a drug that alters these parameters in the opposite direction These results further indicate that the direction of the resulting changes and what agents were used to achieve the local differences are less important Our results are in good agreement with numerous previous investigations which linked an increased ventricular vulnerability to slowed conduction in the ventricle The present study however demonstrated that an increased ventricular vulnerability can also be accompanied by an accelerated conduction in the localized areas which leads to an increase in local differences in the CT In our experiments with K as well as with epinephrine the local dispersion of CT was increased when ventricular vulnerability to fibrillation was high (decreased VFT) and decreased when the ventricular vulnerability was low (increased VFT) The same conclusions can be drawn by analyzing the changes in RP The increased vulnerability was consistently found when the local differences of RP were augmented and decreased when the local differences in RP were small This fact has been shown repeatedly and emphasized in recent years by Moe and Han and colleagues

Local dispersion of ventricular excitability at a given moment is more than local variation of the CT and RP because the time of arrival of propagated impulses is also involved in the actual degree of dispersion of excitability The RT of conducted beats is the electrophysiologic parameter measuring the excitability state of different myocardial areas in a given moment of the cardiac cycle Therefore the local dispersion of RT is the best indicator of local dispersion in ventricular excitability In our experiments the degree of dispersion of CT and RP were always increased with increased ventricular vulnerability and decreased with decreased vulnerability The changes in local dispersion of RT paralleling the changes in ventricular vulnerability were however most apparent Thus the degree in local dispersion of RT or the degree in local dispersion of excitability was the best indicator of ventricular vulnerability to fibrillation Local changes in RP and CT seem to influence the ventricular vulnerability by contributing to the degree of local dispersion of RT and hence to the degree of local disparity of excitability

Summary

In experiments on 16 mongrel dogs conduction time (CT) local refractory periods (RP) and recovery time (RT) of conducted beats were measured in the ventricles under local coronary perfusion and under systemic intravenous infusion with potassium chloride or epinephrine The values of these parameters found in the locally perfused and in the non perfused areas and the degree of local dispersion of these values were correlated with ventricular fibrillation thresholds Regardless of potassium or epinephrine infusion ventricular vulnerability to fibrillation was significantly lower with local infusions than with systemic infusions It was found that changes of CT RP and RT in either direction would occur with increased and decreased fibrillation thresholds and they were not directly correlated to ventricular vulnerability to fibrillation The local dispersion of these parameters between the perfused and non perfused areas however was always increased when ventricular vulnerability was high and decreased when ventricular vulnerability was low These results are strong evidence supporting the importance of local dispersion in excitability The local dispersion was best represented by local variation in the RT of conducted beats which under all experimental conditions correlated best with ventricular vulnerability The other electrophysiological parameters seem

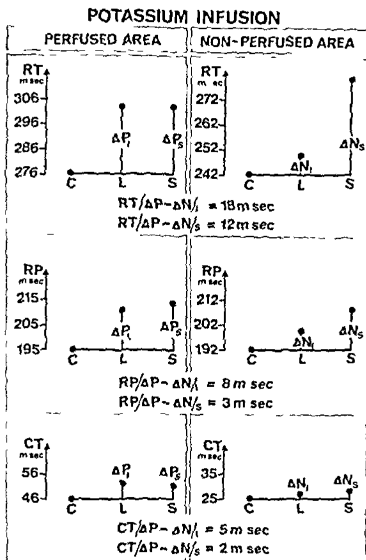


Fig 4 *Increases in the mean values of RT RP and CT from* the control in the perfused and non perfused areas in experiments with potassium infusion C = the control values L = the values during local infusions and S = during *systemic infusions* ΔP = *changes in the perfused area during local infusions and* ΔP = *during systemic infusion* ΔN = changes in the non perfused area during local infusion and ΔNs = during systemic infusion $\Delta P - \Delta N/l$ = the absolute difference between changes in the perfused and nonperfused areas during local infusion $\Delta P - \Delta N/s$ = the difference *during systemic infusion See text for description*

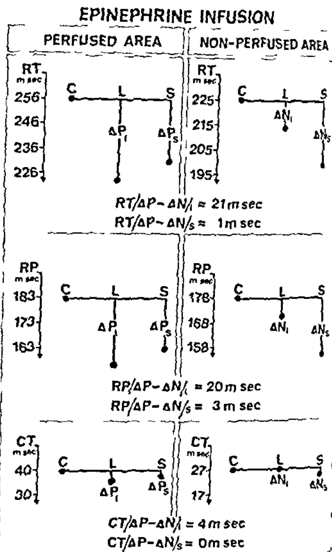


Fig 5 *Decreases in the mean values of RT RP and CT from* the control in experiments with epinephrine infusion Conventions are the same as in *Fig 4* See text for description

slight decreases occurred in other areas On the other hand the dispersion was smaller when the induced decreases occurred in both areas in the same direction and were of similar degree The absolute differences $\Delta P - \Delta N$ was again greater during local infusion of epinephrine

As shown in Fig 2 decreased VFT s (or increased ventricular vulnerability to fibrillation) were always accompanied by increased local dispersion of the electrophysiologic parameters whether it was induced by local perfusion of K or epinephrine The differences in local dispersion between local and systemic infusions ($\Delta P - \Delta N$) was generally more marked for RT than for CT and RP (Figs 4 and 5) It appears therefore that the degree of local dispersion of RT correlates best with ventricular vulnerability to fibrillation

Discussion

It has been shown that hyperkalemia induced locally in the ventricular myocardium increases ventricular ectopic activity and that generalized hyperkalemia of the myocardium suppressed the ectopic activity [10,11] Therefore it is not surprising to observe in the present study that ventricular fibrillation thresholds were significantly lower during the local K infusion than in the control state and during systemic hyperkalemia Similar results were recently reported by Logic [8] who

Perfusion of the canine interventricular septum Significance of right coronary artery supply

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It is traditionally stated that among other differences from the human the canine right coronary artery does not supply the interventricular septum[1] With few exceptions[2,3] the septum and related structures including the atrioventricular node bundle of His and the bundle branches are said to be perfused exclusively by the anterior septal artery and by small perforating branches of the anterior and posterior descending arteries[6] These vessels with the occasional exception of the posterior descending[7] are all branches of the left coronary artery in the dog

During the course of experiments concerning the effects of coronary arteriography on intraventricular conduction[1] we found electrophysiologic evidence suggesting a physiologically significant right coronary artery supply to the canine interventricular septum in 25 per cent of cases Accordingly we undertook a histologic and radiographic investigation to determine the anatomic substrate of this effect

Methods

Eight mongrel dogs of both sexes weighing from 10 to 31 kilograms were heparinized and then killed The hearts were excised and placed in a warm saline bath Within one hour the coronary arteries were cannulated with polyethylene tubing which was ligated in place Both arteries were simultaneously flushed with 37 C Saline solution under 160 mm Hg pressure for 10 minutes followed by a barium and colored gelatin mass[11] under identical conditions The heart was kept in a constant temperature bath at 37 C during injection

After the gelatin mass was set and the heart fixed with cold 10 per cent formalin the atria were removed and contact radiographs of the intact ventricles were made in anteroposterior lateral and apical basal projections using Kodak type SR 54 single emulsion radiographic film (Fig 1) The interventricular septum from the level of the aortic valve ring down to the bases of both papillary muscles was removed The septum was cut into blocks which were sectioned at 6 μ The portion of the septum studied and the plane of sectioning are shown in Fig 1 Each one hundredth section was retained Alternate sections were stained with the elastic Van Gieson stain or with the Goldner modification of the Masson trichrome stain These stains delineate the connective tissue sheath of the intraventricular conduction system The Goldner stain in addition differentially stains ordinary myocardium and the specialized tissue of the conduction system

Different color injection masses were used in the left (red) and right (blue) coronary arteries Since the pigments of the injection mass retain their color through histologic processing and the method visualizes vessels as small as 40 μ the origin of vascular supply to any portion of the septum can be precisely determined by microscopic examination of the histologic sections (Fig 3) The injection masses mix poorly therefore intercoronary anastomoses can be identified by the presence of both colors within the lumen of a single vessel

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to be of importance for the ventricular vulnerability when they contribute to an increased or decreased local dispersion of excitability

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marginal branches before terminating in the right circumflex artery (Fig 1) The relative prominence of these three branches was variable (Table I) In six animals a conus artery of modest size was evident on the radiographs of the intact ventricles The gross distribution of the left and right coronary arteries described above agreed with previous descriptions of the canine coronary circulation (Fig 1) [13]

Ventricular intercoronary anastomoses were grossly evident in seven of eight hearts These occurred within the free wall of the right ventricle near its border with the left ventricle (especially near the cardiac apex) involving the various divisions of the right and left coronary arteries with about equal frequency Macroscopic vessels to the interventricular septum from the right coronary artery were observed in the contact radiographs of six of eight hearts (Fig 1)

Microscopic coronary anatomy Microscopic examination of all eight hearts revealed vessels in the interventricular septum containing blue pigment thus identifying them as right coronary artery tributaries (Figs 3 and 4) In six of eight hearts there were regions in which only right coronary tributaries were found In four specimens (dogs 5 to 8) the area containing only right coronary vessels was small In two specimens (dogs 2 and 3) there was a moderate region of the upper interventricular septum perfused solely by right coronary artery vessels Right coronary artery perfusion always occurred in the upper portion of the interventricular septum (Fig 2) In all eight hearts the volume of septum with only right coronary artery perfusion was smaller than the area containing both left and right coronary artery tributaries and intercoronary anastomoses (Fig 2)

Right coronary artery vessels near the bundle of His were noted in three hearts (Fig 4) In each case left coronary vessels were also observed in close proximity Right coronary supply to the proximal right bundle branch was evident in four hearts and to the left bundle branch in one heart In all cases the fascicles of the left bundle branch and the distal right bundle branch were supplied exclusively by the left coronary artery principally by the anterior septal artery

Discussion

Although previous reports have mentioned occasional right coronary artery supply to the

Table I Patterns of right coronary artery branching Terminal branches are graded from + (small) to + + + (large)

DOG	RAV	RAM	RC
1	+ +	+	+ + +
2	+	+ + +	+
3	+ + +	+	+
4	+ +	+ +	+ +
5	+ + +	+ +	+
6	+ + +	+ +	+ + +
	+	+ + +	+ + +
8	+ + +	+ +	+ +

Abbreviations RAM = right acute marginal RAV = right anterior ventricular RC = right circumflex
conus branch present

membranous' or muscular interventricular septum we found this to be more extensive than has been previously noted Breed variation' in coronary anatomy cannot have been a factor in the difference between our results and previous reports since the animals we used were unselected mongrel dogs Right coronary vessels were large enough to be visible on contact radiographs in six of eight hearts (Fig 1) Microscopically demonstrable right coronary vessels were found in the upper interventricular septum of all eight hearts (Figs 2 and 3) In two hearts only microscopic right coronary perfusion was seen These vessels may represent continuations of intraatrial right coronary artery branches which course down into the upper portion of the interventricular septum

The suitability of the dog as the subject of experiments involving the coronary circulation has been questioned [1] Nevertheless it remains the most widely used experimental animal in investigations involving coronary arteriography [11,14] and the effects of myocardial ischemia and reperfusion upon electrophysiology [1,2] metabolism [1,2] hemodynamics [2,7] and radionuclide cardiac imaging [2]

Coronary arteriography is the most direct and unequivocal means of separating the physiologic distribution of the two coronary arteries Functional distribution of effective perfusion from each coronary artery can be determined by injecting contrast media or other substances into either coronary artery and assessing the distribution of electrophysiologic or other end point effects From our studies of the electrophysiologic effects of coronary arteriography it was clear that

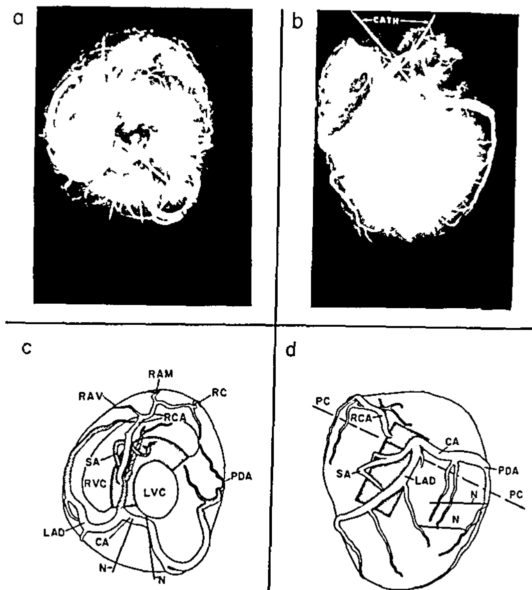


Fig 1 Contact radiographs and corresponding diagrams following barium gelatin injection in right and left coronary arteries *a* and *c* contact radiograph and corresponding diagram in the apical-basal projection demonstrating typical anatomy of the right coronary artery *(RCA)* and the left coronary artery and its branche Note the position of the interventricular septum *(shaded crescent)* and the cavities of the right ventricle *(RVC)* and left ventricle *(LVC)* The shaded area of the septum was subsequently removed for histologic examination Electrode needles *(N)* in the left ventricular wall are incidentally noted *b* and *d* contact radiograph and corresponding diagram in the anteroposterior projection The plane of the interventricular septum is represented by the shaded rectangular area The dotted horizontal line *(PC)* represents the plane of cutting for the histologic examinations of the septum Note the position of the coronary catheters *(CATH)* on the contact radiograph In *a* and *b* the terminal branch of the right circumflex coronary artery *(RC)* can be seen coursing to the region of the interventricular septum Abbreviations *CA* = left circumflex *LAD* = left anterior descending *PDA* = posterior descending *RAM* = right acute marginal *RAV* = right anterior ventricular *SA* = septal artery

Reconstruction of regional septal perfusion was made from drawings of each histologic section which were transcribed upon diagrams of the interventricular septum (Fig 2)

Results

Gross coronary anatomy The left main coronary artery was short in all hearts and divided within a few millimeters of its origin into the left anterior descending, circumflex and anterior septal arteries In six hearts the anterior septal artery arose from the left main coronary artery, in one from the left anterior descending and in one from the circumflex artery The latter terminated in all hearts as a prominent posterior descending artery, which was larger than the left anterior descending artery in two cases smaller in one and of equal size in five

The right coronary artery had a long common trunk and gave off anterior ventricular and acute

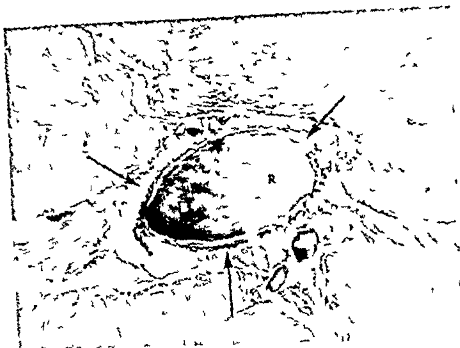


Fig 3 Photomicrograph of a section of septal myocardium (Van Gieson stain) from Dog 1 following colored barium gelatin injection of the coronary arteries. In the original color photomicrograph the artery visualized (arrows) had red (R) and blue (B) pigment indicating mixed right and left coronary artery perfusion. This vessel is a branch of the septal artery of the left coronary and indicates the existence of anastomoses between the right coronary artery and the septal artery

tory of regional septal motion during infarction and early reperfusion disclosed that the upper portion of the septum suffers less dyskinesis than the middle and lower septal regions during ligation and release of the left anterior descending artery distal to the anterior septal branch. This suggests that there is less ischemia of the upper septum, perhaps due to more collateral blood flow. Although the anterior septal and posterior descending arteries probably contribute significant alternative perfusion to the entire septum, the better tolerance of the upper septum may be a reflection of right coronary artery supply with greater total perfusion of this region

The course of the specialized cardiac conduction tissue is similar in humans and dogs. The canine A V node and the bundle of His have been considered to be perfused solely from the left coronary artery by the anterior septal artery and posterior septal branches of the posterior descending artery. However right coronary artery supply to the A V node has been described. Experiments by Lumb and co-workers showed that after complete ligation of the anterior and posterior septal arteries only 79 per cent of animals displayed electrocardiographic evidence of heart block. Ligation of the anterior septal artery alone produced heart block in 64 per cent, while ligation of the posterior septal artery alone produced heart block in 57 per cent. Since often all other tissue was necrotic in regions containing viable conduction tissue, intrinsic properties of the conduction tissue must have contributed to its preservation. Their results and our demonstration of right coronary artery supply to the bundle of His in 38 per cent of dogs may indicate that in this group right coronary artery perfusion is sufficient to maintain the functional and anatomic viability of the interventricular conduction system

The right coronary artery supply to portions of the proximal intraventricular conduction system described herein has not been previously reported. This may be because injection material suitable for studying the origin of very small vessels (such as canine intercoronary anastomoses) has only recently become available. New information concerning the blood supply to the human conduction system has also resulted from this technical advance

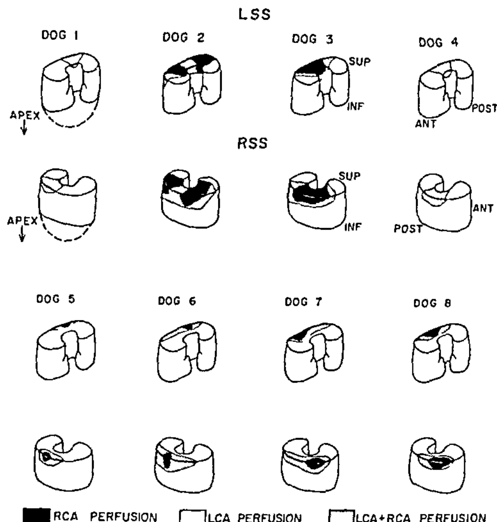


Fig 2 Diagrams of the interventricular septum illustrating the coronary perfusion pattern based on histological examinations in eight dogs The diagrams are oriented for visualization of the left septal surface *(LSS)* in the first and third rows and for the right septal surface *(RSS)* in the second and fourth rows The septum is further defined in its superior *(SUP)* inferior *(INF)* anterior *(ANT)* and posterior *(POST)* aspects and the apex is indicated by dotted lines Areas perfused solely by the right coronary artery *(RCA)* are indicated in black while left coronary perfusion *(LCA)* is indicated in white Mixed right and left coronary perfusion is demonstrated by the shaded areas It can be seen that there is right coronary perfusion in the upper interventricular septum of all eight hearts

contrast media injected into the right coronary artery affected portions of the left bundle branch in 25 per cent of dogs This result is reminiscent of the changes in left sided conduction which may be seen in most humans undergoing right coronary arteriography [30] A study by Hildner and co workers[17] affords the same conclusion since transient 2 1 AV block and complete heart block localized to the bundle of His occurred after right coronary arteriography with Renografin M 76 (methylglucamine diatrizoate 76 per cent buffered with N methyl glucamine) in one of 10 animals In this case septal perfusion from the right coronary artery can be inferred from electrophysiologic effects referable to the bundle of His In addition changes in T wave and ST segment which could be due to ventricular or septal intercoronary communications were observed after right coronary arteriography with Renografin 76 or M 76 in 30 per cent of dogs [1] In the dog contrast medium might reach its site of action through previously described ventricular intercoronary anastomoses [6, 8, 5] However two more direct routes are suggested from the current study—that is intraseptal coronary communications (Fig 3) or direct right coronary artery supply to the conduction system within the interventricular septum (Fig 4)

The possible effects of septal perfusion by the right coronary artery after coronary artery ligation are more difficult to interpret since commonly only a single branch is interrupted However since this is an active area of research it deserves further comment Studies in our labora

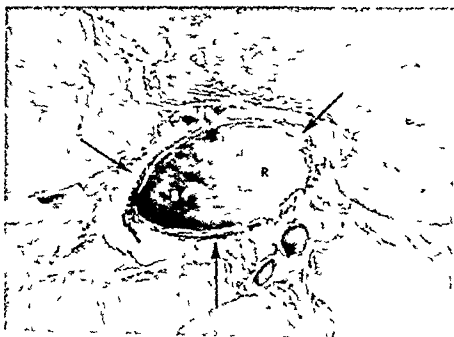


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Fig 4 Photomicrograph of the region of the bundle of His *(HB)* after modified Masson trichrome stain demonstrating mixed right and left coronary perfusion In the original color photomicrograph right coronary artery perfusion was indicated by the presence of blue vessels *(RCA arrows)* which appear black in this figure Left coronary artery perfusion was indicated by the presence of red vessels *(LCA arrows)* The left bundle branch *(LBB)* and the right bundle branch *(RBB)* are visible as is a portion of the septal myocardium *(SM)* Perfusion of the canine conduction system by the right coronary artery has not previously been reported

The physiologic significance of right coronary artery perfusion to the intraventricular conduction system can only be speculated upon from retrospective analysis of experiments undertaken without considering this factor Although the method of injection and histologic examination which we used gives precise information concerning detailed vascular supply to the interventricular septum it provides only a *qualitative* estimate based upon subjective reconstruction from histologic sections of the volume of tissue perfused from the right coronary artery No quantitative information can be gained concerning origin or amount of blood flow to a given volume of tissue Coronary arteriography with radionuclide labelled microspheres[36, 37] could give semiquantitative blood flow and volume of distribution information under relatively physiologic conditions

Our work indicates that previous concepts concerning the distribution of the right coronary artery to the interventricular septum and the specialized conduction system contained therein are incomplete The canine coronary system is of course, left dominant, and the septal artery far more prominent than in the human heart However, the canine right coronary artery provides potentially significant perfusion to the interventricular septum and may be an important source of collateral flow to the upper septum The canine interventricular septum is therefore less suitable for experimental studies of ischemia and infarction than is the free wall of the left ventricle Investigations which involve the canine interventricular septum should describe and account for both right and left coronary artery perfusion of the region studied

Summary

The perfusion of the canine interventricular septum was studied by the method of postmortem injection of a colored barium-gelatin mass with radiographic and histologic examination of specimens These studies demonstrated distributions of the right and left coronary arteries similar to those described by other workers with two significant exceptions First radiographically visible vessels were seen coursing from the right coronary artery to the upper portion of the interventricular septum Second histologic demonstration of right coronary artery perfusion to the upper interventricular septum (in some cases including the specialized conduction tissue contained therein) and intercoronary anastomoses within the interventricular septum were observed Right coronary artery supply to the septum was more frequent and of greater magnitude than previously described These results may explain certain data pertaining to experimental myocardial ischemia and to coronary arteriography and suggest a functionally important role for the right coronary artery supply to the canine septum These considerations render it imperative that the vascular supply to the canine interventricular septum be considered in experiments involving the coronary circulation and the septum Some

investigations demand a single vascular supply to a particular region of interest The canine interventricular septum can no longer be considered in this category

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A proposed pathogenesis of cor triatriatum: Impingement of the left superior vena cava on the developing left atrium

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Cor triatriatum[1] is an uncommon malformation of the heart in which the left atrial chamber is subdivided into two compartments by an abnormal accessory membrane. Typically the partition lies diagonally in the left atrium and separates the portion containing the pulmonary venous return from the part with the left atrial appendage and mitral valve. Concepts of the mode of development of the malformation have involved either an abnormality of development of the atrial septum, 'malseptation hypothesis',[6] a failure of incorporation of the pulmonary vein into the left atrium, 'malincorporation hypothesis,'[7-12] or a combination of these ideas, the 'entrapment hypothesis.'[13]

Observation of patients with cor triatriatum at autopsy suggested to us that the posterior attachment of the abnormal membrane to the left atrial wall bore a close relationship to the course of the left superior vena cava. Accordingly we reviewed the morphological features of hearts with cor triatriatum and for comparison studied hearts with so called cor triatriatum dexter and serial histological sections of normal human embryos. The results suggest that the abnormal membrane that constitutes cor triatriatum is induced by the left superior vena cava impinging upon the developing left atrium.

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Observations

The patients in the autopsy files of The Johns Hopkins Hospital with cor triatriatum whose hearts were available for review are listed in Table I. The cases have been divided into those five with cor triatriatum of the left atrium (classical cor triatriatum), four with a form of cor triatriatum where the abnormal membrane isolates only the left atrial appendage from the remainder of the left atrial cavity (cor triatriatum variant), and three cases with a membrane dividing right atrium (cor triatriatum dexter).

Cor triatriatum of the left atrium. The five cases with classical cor triatriatum had the left atrial cavity divided into two compartments by the abnormal membrane (Figs. 1 and 2). The posterior-superior cavity contained the pulmonary venous drainage which was normal in all instances. The left atrial appendage arose from the anterior inferior cavity in all five and the mitral valve in three. Two hearts (Cases 4 and 5) had mitral atresia, one associated with aortic atresia. In each of the five hearts the interatrial septum had both septum primum and septum secundum components in the usual relationship to each other. The septum secundum and the margins of the fossa ovalis were normal in all. The septum primum, seen as the valvulus of the fossa ovalis, showed fenestration in two (Cases 2 and 3) and showed eversion of its free margin into the right atrium in the two hearts with mitral atresia.

A consistent finding in all five specimens was the presence of patent or persistent left superior vena cava (PLSVC). This vessel ran its usual course, joined the coronary sinus, and joined the right atrium at the ostium of the coronary sinus. Of particular note was the relationship of the

Table I Patients with cor triatriatum

Case no	Age/sex	Clinical features	Other pathological features
I Cor triatriatum of the left atrium			
1	9 yr F	Normal gestation Cardiac cath pul hypertension coarctation of aorta DeBakey graft post-op low output right sided failure and pulmonary edema	Persistent left superior vena cava (PLSVC)
2	10 mo F	Normal gestation dyspnea cyanosis systolic murmur cardiomegaly congestive heart failure	Right atrial and ventricular hypertrophy Fenestrated foramen ovale Bicuspid aortic valve PLSVC
3	13 mo F	Diabetic mother premature birth cardiac cath atrial and ventricular septal defects bilateral peripheral pulmonic stenosis Resp distress tachycardia and cyanosis Arrhythmias	Fenestrated foramen ovale ventricular septal defect PLSVC
4	2 days F	Normal gestation cyanosis cardiomegaly pulmonary congestion congestive heart failure	Mitral and aortic atresia patent foramen ovale patent ductus arteriosus coarctation of aorta PLSVC
5	10 mo M	Mongolism cyanosis Fluoroscopy biatrial enlargement tachycardia left sided failure	Mitral atresia single ventricle bicuspid pulmonic valve patent foramen ovale PLSVC
II Cor triatriatum of the left atrial appendage			
6	3 yr M	Cyanosis dyspnea cardiac cath Tetralogy of Fallot left Blalock Taussig anastomosis convulsions cardiopulmonary arrest	Tetralogy of Fallot pulmonary congestion PLSVC
	4 yr F	Cyanosis cardiac cath Tetralogy of Fallot left and right Blalock Taussig anastomoses pulmonary edema	Tetralogy of Fallot Patent foramen ovale PLSVC
8	5 yr M	Normal gestation cyanosis cardiac cath Tetralogy of Fallot total correction shock acidosis cardiopulmonary arrest	Tetralogy of Fallot PLSVC
9	4 mo M	Cyanosis cardiac cath double-outlet right ventricle pulmonic stenosis failure to grow hypoxemia terminal aspiration	Double outlet right ventricle ventricular septal defect infundibular pulmonic stenosis unicuspid pulmonary valve PLSVC
III Cor triatriatum of the right atrium			
10	9 mo F	Cyanosis cardiac cath pulmonary stenosis and single ventricle Potts anastomosis congestive heart failure	Fenestrated foramen ovale dilated left atrium small right ventricle ventriculoseptal defect tricuspid atresia
11	8 yr F	Chronic ethanol abuse subdural hematoma diabetes insipidus pneumonia	Heart otherwise normal
12	6 yr F	Cholecystectomy ulcerative colitis degenerative joint disease chemical diabetes	Slight left ventricular hypertrophy

path of the PLSVC over the left atrium In each of the five hearts the abnormal membrane subdividing the left atrial cavity was attached to the endocardial aspect of the atrium just under the course of the PLSVC

Cor triatriatum of the left atrial appendage In view of the consistent finding of PLSVC with the classical form of cor triatriatum we reviewed the remainder of the 70 hearts with PLSVC available in the autopsy files of The Johns Hopkins Hospital to see if any other examples had been overlooked It became apparent that there was a variation of cor triatriatum in which the cavity of the left atrial appendage is partially or completely separated from the remainder of the left atrial cavity by an abnormal membrane

The four patients described in Table I all had a persistent LSVC which pursued a course over the left atrium somewhat more to the left than that seen in the hearts with classical cor triatriatum In this variant form of cor triatriatum the PLSVC ran across the area of the junction of the left atrial appendage with the body of the atrium The abnormal stenosing or as in one instance occluding membrane was found just beneath the course of the PLSVC (Fig 3)

Cor triatriatum of the right atrium Three hearts with right atrial membranes corresponding

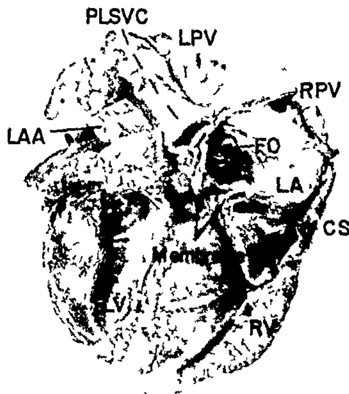


Fig 1 The heart from Case 4 viewed from the posterior aspect The left ventricle (*LV*) has been opened along the obtuse margin The membrane which divides the left atrium (*LA*) into two chambers originates along the line of the persistent left superior vena cava (*PLSVC*) which drains into the coronary sinus (*CS*) The right (*RPV*) and left pulmonary veins (*LPV*) drain into the chamber which also contains the fossa ovalis (*FO*) lying posterior-superior to the membrane The left atrial appendage (*LAA*) and mitral valve are constituents of the anterior-inferior chamber of the LA The right ventricle (*RV*) is hypertrophied

to so called cor triatriatum dexter were available for examination (Fig 4) The membranes one intact (Case 10) two fenestrated (Cases 11 and 12), were clearly originating from the crista terminalis of the right atrial wall In none of the three cases was a PLSVC present

The membrane which forms cor triatriatum dexter must be distinguished from large valves of the inferior vena cava or coronary sinus These structures may be fenestrated or cord like in part but do not show origin from the crista terminalis

Embryological studies To determine the relationship of the LSVC to the developing left atrium and the time of its involution relative to the development of other structures in the atria we reviewed serial histological slides from nine normal human embryos of stages 14 to 21 and three early fetuses of 34 36 and 45 cm crown-rump lengths which covered the range of approximately four to 10 weeks gestation

Details of the preparation of most of the specimens have been presented previously [11] The left and right anterior vena cava are of approximately equal size at stage 14 By stage 16 however the terminal portion of the LSVC which is closely related to the left atrium is relatively smaller than the right (Fig 5) In late embryonic stages the LSVC is much smaller than the right (Fig 6) and by early fetal development it becomes obliterated except for the portion forming the coronary sinus

The time of development of the interatrial septae fusion of pulmonary veins to the posterior left atrium and junction of septae and atrioventricular cushion material observed by us corresponds to the descriptions of others [15, 16] The structure which becomes the crista terminalis of the right atrium is derived from the septum spurium which also forms the right valve of the sinus venosus of the embryonic heart The septum spurium is present at stage 14 and is related to the right lateral margin of the indentation of the atrium by the outflow tract portion of the primary heart tube With subsequent growth and development of the heart the septum spurium becomes relatively less prominent but persists as the crista terminalis of the normal mature heart

Discussion

We describe five hearts with classical cor triatriatum of the left atrium and four with a variant where the left atrial appendage is separated from the remainder of the left atrial cavity In all nine specimens a persistent left superior vena cava was present and coursed over the atrium at a site corresponding to the line of attachment of the abnormal intra atrial membrane The consistent relationship of the PLSVC to the membrane s insertion despite variations in the course of the PLSVC suggests that the PLSVC may in some manner induce formation of the membrane

In three hearts with cor triatriatum dexter we observed that the abnormal membrane in the right atrial cavity is simply an accentuation of the crista erminalis or persistence of the septum spurium and the embryonic right venous valve The adult crista terminalis is derived from the embryonic septum spurium and right valve of the sinus venosus Our study of serial histological sections of normal human embryos suggested

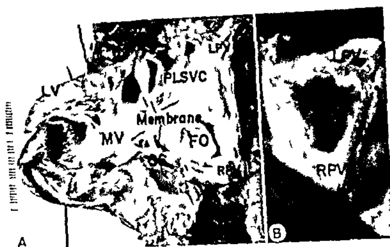


Fig 2 *A* Heart from Case 1 opened in a manner similar to that shown in *Fig 1* In this example the fossa ovalis which has a fenestrated valvulus extends into both of the chambers created in the left atrium by abnormal membrane *B* The left atrium has been reapproximated and the stenotic opening created by the membrane is seen from the posterior superior chamber of the left atrium which receives the pulmonary venous drainage Note that the wall of this chamber consists of atrial muscle a finding which was present in all the cases of cor triatriatum



Fig 3 *A* Heart from Case 7 opened along obtuse margin and viewed from the posterior aspect as in *Figs 1 and 2A* A probe passes through the persistent LSVC into the coronary sinus *B* The left atrium has been opened and rotated so as to demonstrate the membrane arising along the course of the PLSVC which separates the cavity of the left atrial appendage from the left atrium A small orifice *(arrow)* in the abnormal membrane is the only communication between the two chambers

that the septum spurium was normally induced by impingement of the outflow tract portion of the cardiac tube against the developing right atrium The partial encirclement of the atrial structure by the downstream end of the heart produces a crease or fold which persists as a distinct structure in the atrial wall The histological observations suggest that at the point of the indentation of the atrial wall there is a local accumulation of cardiac jelly which as it becomes organized as part of the gelatinous reticulum of the heart may contain cardiac muscle or mesenchymal elements Once cellular constituents appear in the fold it continues to grow and forms the membrane of the septum spurium

From considerations of the embryos studied it seems possible to us that if the LSVC is unusually large or is persistent that it may impinge on the left atrial wall in a manner similar to that observed in the indentation and membrane induction in the right atrium by the overlying cardiac tube Such an indentation by the LSVC at an

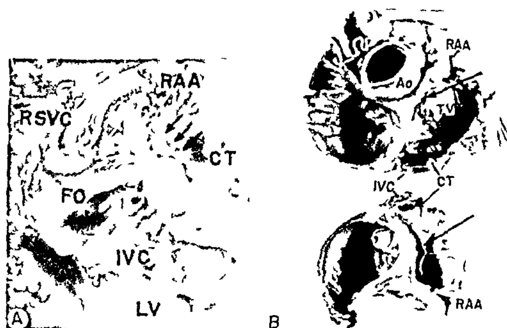


Fig 4 *A* Heart of Case 10 with cor triatriatum dexter The abnormal membrane *(arrows)* is arising from the crista terminalis *(CT)* The right atrial appendage *(RAA)* is normally positioned but the tricuspid valve is atretic *B* Heart of Case 12 with cor triatriatum dexter The abnormal membrane is merely a fenestrated cord arising from the crista terminalis

early stage could lead to similar local accumulation of cardiac jelly cellular proliferation, and membrane formation in the left atrium

Not every PLSVC necessarily leads to cor triatriatum In the 70 examples of PLSVC reviewed by us nine (13 per cent) were associated with an underlying abnormal membrane However every such abnormal left atrial membrane seen by us was associated with a PLSVC It is of course possible that the LSVC could induce the membrane of cor triatriatum and then subsequently undergo a normal obliteration The reason that the majority of persistent LSVC s do not induce an abnormal membrane is unknown Membrane induction may be a function of the depth of impingement of the LSVC into the left atrium and the relationship may be determined by other factors such as associated malformations

Since the first observation of cor triatriatum [1] various hypotheses have been presented to account for the morphogenesis of the anomalous intra atrial septum These can be divided into three main groups

1 The malseptation hypothesis—the abnormal growth of the septum primum The malseptation hypothesis has been proposed in a variety of forms An overgrowth of the valve of fossa ovalis which is displaced laterally until it becomes adherent to the outer wall of the left atrium has been suggested [3] Borst,[4] who coined the term cor triatriatum thought that the common pulmonary vein insertion is displaced to the right between the two septa and the pressure of the blood returning to the heart gradually pushes the septum primum to the left The septum primum would become the persistent diaphragm and the septum secundum the interatrial septum [5] Similarly Helwig[6] proposed that the anomalous membrane might be caused by a separation of the primary and secondary septa leading to a partial division of the left atrium

The malseptation hypothesis does not fully explain cor triatriatum in that if septum primum were the anomalous diaphragm its growth should be arrested so that it would not fuse with the endocardial cushions and one would expect a defect in the interatrial septum of the ostium primum variety In all cases which we studied the interatrial septum when viewed from the right atrium had a foramen ovale (though probe patent or fenestrated at times) which was normal in structure with a well defined limbus in the left atrial portion This observation demonstrates that septum primum and septum secundum retain their normal positions relative to each other in cor triatriatum

2 Malincorporation hypothesis—failure of the incorporation of the pulmonary vein into the left atrium By far the most widely accepted this hypothesis was first expressed by Hagenauer[7] who suggested that the junction between the left

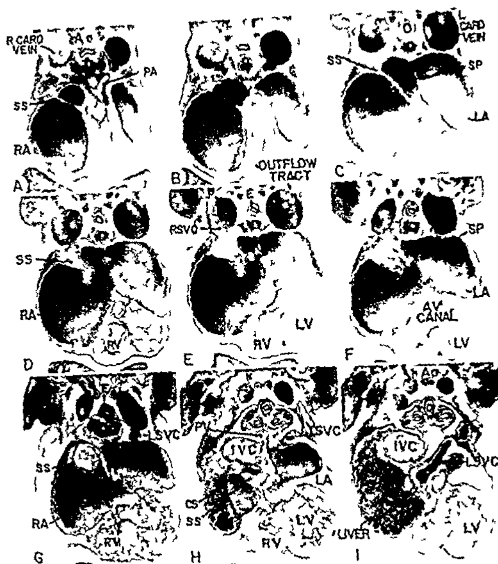


Fig 5 Selected serial histological sections from a normal stage 16 human embryo The sections proceed from cranial toward caudal levels through the region of the developing heart Paired dorsal aortae (Ao) and cardinal (Card) veins are present at all levels The outflow tracts from the right and left ventricles are not yet anatomically separated The septum spurium (SS) can be seen in relation to the right lateral margin of the outflow tract where it indents the developing atria in panels A C At levels D C the septum spurium is a prominent membrane bordering the channel of venous return to the right atrium from the right superior vena cava (RSVC) and the inferior vena cava (IVC) At level H the septum spurium fuses with the dorsal atrioventricular (AV) cushion material after passing along the right inferior margin of the mouth of the coronary sinus (CS) which drains the left superior vena cava (LSVC) Slight indentation of the left atrium by the LSVC is seen in panel F and C At level H the pulmonary vein (PV) enters the posterior aspect of the left atrium in the area encircled by the LSVC draining into the coronary sinus It is postulated that when the LSVC is unusually large or persistent it may indent the left atrium and give rise to an abnormal membrane which divides the left atrium into two chambers One chamber would contain the pulmonary venous return the other the left atrial appendage and mitral valve The process may resemble the induction of the septum spurium by the outflow tract indenting the right atrial wall Persistence or prominence of the septum spurium which normally becomes the crista terminalis appears to account for cor triatriatum dexter (All Verhoeff and van Gieson s stain original magnification ×?0)

atrium and the common pulmonary vein is at an acute angle and that with dilatation of the sinus venosus the common pulmonary vein is compressed and its mouth eventually obliterated by adhesions which become the membrane Loeffler and Edwards and associates concluded that the anomalous septum is the primitive wall of the left atrium Griffith attributed the anomalous septum to a failure in the complete amalgamation of the part of the atrium which is said to be

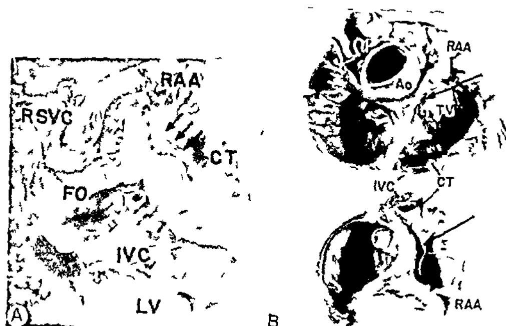


Fig 4 A Heart of Case 10 with *cor triatriatum dexter* The abnormal membrane *(arrows)* is arising from the crista terminalis *(CT)* The right atrial appendage *(RAA)* is normally positioned but the tricuspid valve is atretic *B* Heart of Case 12 with cor triatriatum dexter The abnormal membrane is merely a fenestrated cord arising from the crista terminalis

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observation of atrial muscle in the posterosuperior chamber between the pulmonary venous ostia[17] as was present in all our cases Further more if the above hypothesis were correct one would expect to find the foramen ovale only in the anteroinferior chamber whereas in many cases the foramen ovale is found in the posterosuperior chamber A similar observation was made by Thilenius and colleagues [1] For example in our Case No 4 (Fig 1) the foramen ovale is in the same chamber as the pulmonary venous return and in Case No 1 (Fig 2) there is a right atrial communication with both left atrial chambers through a fenestrated valvulus of the foramen ovale

3 *Entrapment hypothesis—an attempt to incorporate the previously stated theories* Van Praagh and Corsini suggested that cor triatriatum results from the entrapment of the left atrial ostium of the common pulmonary vein by tissue of the right horn of the sinus venosus from which septum primum develops leading to the failure in the incorporation of the common pulmonary vein into the left atrium during the fifth embryonic week As an attempt to incorporate the previously mentioned hypotheses it suffers from an incorporation of their weaknesses and is in addition at odds with the concept of interatrial septation developed by most observers Furthermore if this hypothesis were correct one would expect two left atrial chambers a posteroinferior and an anterosuperior whereas in our observations and those of other investigators the anomalous intra atrial septum almost invariably divides the left atrium into a posterosuperior and an anteroinferior chamber

The morphogenesis of the anomalous membrane subdividing the right atrial cavity has also been controversial Previous reports have described several varieties of cor triatriatum dexter However if prominent valves of the inferior vena cava or coronary sinus are excluded the remaining cases described resemble the three hearts reported here in having the abnormal membrane arising from the crista terminalis Cor triatriatum dexter may simply be considered to be persistence of an unusually prominent septum spurium and right valve of the sinus venosus

In an attempt to classify cor triatriatum James has described four categories His Types I and III correspond to classical cor triatriatum and cor triatriatum dexter respectively as used in this study His Type II is total anomalous pulmonary venous drainage to the coronary sinus and Type IV is atrial diverticulum Since there is no abnormal intra atrial membrane such as characterizes cor triatriatum in the latter two categories it is difficult to see any anatomical embryological or pathophysiological justification for including anomalous pulmonary venous return and atrial diverticulum in the entity cor triatriatum We feel that less confusion would be created if the term is confined to those cases where the left atrial cavity is subdivided by an abnormal membrane arising in relationship to the course of the left superior vena cava The uncommon cardiac malformation with a constricting ring located above the mitral valve appears to arise by a different pathogenetic mechanism [21]

In conclusion the study has shown that there is a close anatomic and probably a close developmental relationship between a persistent left superior vena cava and cor triatriatum of the left atrium (Fig 7) A hitherto undescribed anatomic variant of cor triatriatum in which the left atrial appendage alone is separated from the atrial cavity also showed a consistent relationship between a persistent left superior vena cava and the abnormal membrane Cor triatriatum dexter appears to be caused by prominence of the embryonic septum spurium and the right valve of sinus venosus a structure which is induced in the embryonic right atrium by impingement of the overlying primary heart tube on the developing atrium By analogy we interpret the abnormal left atrial membrane of cor triatriatum as being induced by impingement of a prominent or persistent left superior vena cava on the developing left atrium

Summary

The development of the abnormal membrane which constitutes cor triatriatum has been controversial variably attributed to the maldevelopment of interatrial septae or to malincorporation of pulmonary veins To examine the hypothesis that the membrane arises in relationship to the left superior vena cava (LSVC) we reviewed our 12 hearts with cor triatriatum and compared serial histological sections of nine normal human embryos of stages 14 to 21 and three early fetuses Of the 12 hearts five had classical cor triatriatum with a membrane dividing the left atrium into two compartments

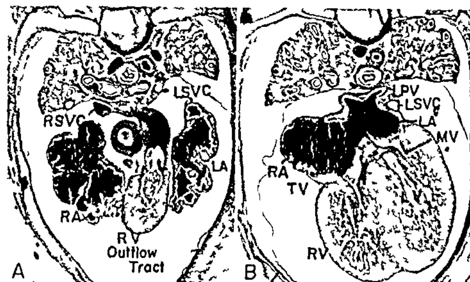


Fig 6 Two serial histological sections from a stage 20 normal human embryo The LSVC is much smaller than the RSVC at *level A* At *level B* the relationship of the LSVC to the developing left atrium is clearly seen Soon after this stage of development the LSVC becomes obliterated except for that portion which constitutes the coronary sinus (Both Verhoeff and van Gieson s tain original magnification ×20)

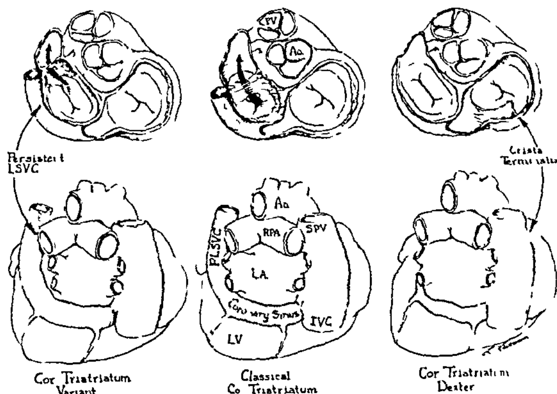


Fig 7 Diagram showing the relationship of the persistent left superior vena cava to the posterior aspect of the heart and to the abnormal left atrial membrane in classical cor triatriatum and the variant of cor triatriatum where the membrane separates the cavity of the left atrial appendage from the remainder of the left atrium Cor triatriatum dexter is a prominence of or a membrane arising from the crista terminalis which forms from the septum spurium of the embryonic right atrium

derived from the confluent portions of the pulmonary veins and that derived from the left hand division of the common auricle of the embryonic heart Parsons [11] after analyzing the previously recorded cases asserted that the septum is due to a defect at the junction between the common pulmonary vein and the right atrium due to a developmental arrest late in the second month of life

Though the malincorporation hypothesis satisfactorily explains the normal appearance of the foramen ovale it is not compatible with the

Spontaneous heart rate, ventricular tachycardia, and the response to procainamide during acute ischemia

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The role of heart rate in the genesis of ectopic activity during experimental myocardial ischemia has been recently emphasized[1,2] Induction of accelerated heart rate may predispose to ventricular tachycardia and fibrillation although the absolute level at which this effect occurs is not settled However the effects of spontaneous heart rate ranging from normal to rapid sinus tachycardia has not been studied in relation to the development of arrhythmias during acute experimental myocardial ischemia Moreover despite previous reports on the efficacy of procainamide in correcting ventricular tachycardia during the early phase of ischemia[3,4] this agent was found to be ineffective during pacing induced arrhythmia[1]

The present study was performed in an anesthetized closed chest animal model to evaluate whether resting sinus heart rate is an important determinant of ventricular arrhythmias during the initial 15 minutes of acute ischemia a period in which there is a high incidence of spontaneous ventricular arrhythmias[6] The response of ventricular tachycardia to therapy with procainamide was compared with untreated animals having a similar extent of ischemia

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Methods

Healthy male mongrel dogs weighing 20 to 25 kilograms were anesthetized with morphine sulfate 3 mg/Kg body weight and pentobarbital 12 mg/Kg body weight After insertion of an endotracheal tube respiration was regulated with a Harvard respiratory pump so as to maintain arterial oxygen saturation and pH in the normal range Animals were placed in the right lateral decubitus position and were studied within 3 to 4 hours after anesthetic induction without opening the chest The precordium was shaved for the purpose of electrocardiographic mapping using 20 surface electrodes at 2 cm intervals in the third fourth and fifth left intercostal space The surface ECG mapping utilized in this study had been found to be a reliable method for quantitating myocardial injury after coronary occlusion and is comparable to the epicardial ECG technique[7] Control tracings taken prior to occlusion did not show any ST elevation After coronary occlusion ST segment elevations of more than 0 1 millivolts were included The number (N-ST) and the sum of ST segment elevations in millivolts (ΣST) were used as indices of the magnitude of ischemic injury

The right carotid artery was isolated through an incision in the neck A double lumen No 5F catheter with a distal lumen was positioned in the proximal 1 5 cm of the left anterior descending coronary artery under fluoroscopic control The balloon was inflated gradually over a period of 60 seconds Aortic pressure peripheral coronary pressure and ECG Lead 1 were continuously monitored Catheters were connected directly to a Statham strain gauge transducer (P23Gb) and

one chamber with pulmonary veins and one with mitral valve and atrial appendage In each heart a persistent LSVC ran along the line of insertion of the membrane All five had normal pulmonary veins and normally located interatrial septae Four hearts with a previously undescribed variant of cor triatriatum had a membrane separating the left atrial appendage from the main left atrial cavity and in each instance the LSVC ran along the line of insertion of the membrane Three hearts had cor triatriatum dexter with a membrane which partially subdivided the right atrium into two chambers The abnormal membrane dividing the right atrial cavity was interpreted as a retention of the septum spurium or right venous valve an embryological structure which becomes the crista terminalis of the fully developed normal heart Embryological studies showed that the LSVC courses along and may indent the left atrium where the abnormal membrane is virtually always located, but that normally the LSVC obliterates during early atrial development The results suggest that cor tria triatum arises through induction of an abnormal left atrial membrane by impingement of a promi nent or persistent LSVC

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Table I Heart rate and aortic pressure responses to ischemia

Group	No	*Mean heart rate*		*Mean aortic pressure*	
		Control	*Ischemia*	*Control*	*Ischemia*
A	19	90 3 ± 2.8	104 1 ± 4 4	112 3 ± 4 1	109 1 ± 3 7
B	30	124.5 ± 1 6	13_0 ± 3 9	11 5 ± 4 9	115 3 ± 3.?
C	?3	155 7 ± 1 5	149 7 ± 5 1	1?1 6 ± 3 9	112.0 ± 4 4
D	10	19? 1 ± 6 1	1?9 4 ± 5 9	1?6 7 ± 7 6	119 ? ± 8 5

P < 0 0? compared to control.

noteworthy that while Group A had a modest rate rise during ischemia this group had a some what lower incidence of arrhythmias and fibrilla tion That sinus rate increments can be relatively innocuous has been illustrated in the unanesthe tized dog undergoing acute ischemia The production of sinus tachycardia by treadmill exercise evoked no arrhythmia during early ischemia when the rate rose to 176 ± 16/minute Ventricular tachycardia and fibrillation were seen at sinus rates of 218 ± 22/minute which is higher than the average for Group D animals of this study

Although rapid sinus tachycardia is probably not frequent in hospitalized patients with infarc tion it is likely that substantial tachycardia occurs in some individuals during the early prehospital phase Moreover infarction in humans may be complicated by more variable levels and extent of ischemia preexistent infarc tion hypertrophy heart failure and age Nevertheless recent data suggest that in the initial 24 hours ventricular tachycardia is not more frequent in subjects with sinus tachycardia compared to those with a normal sinus mecha nism

In this study several other factors which may affect arrhythmia incidence during experimental ischemia such as size of ischemic area and aortic pressure [?] have been taken into consideration The latter appears to affect arrhythmia incidence only when there are acute reductions of pres sure [?] In these animals in which the balloon occlusion was placed approximately 1 5 cm from the origin of the anterior descending artery there was no significant difference in the extent or severity of the ischemia as judged by precordial mapping The failure to observe a significant difference in area of injury may be related to the fact that animals with high resting heart rate

Table II Relation of resting heart rate to ST segment change

Group	*No*	*HR†*	*N-ST†*	*ΣST†*
A	16	?0-10?	10 50 ± 0 55	5.29 ± 1 13
B	??	106-140	11 31 ± 0 47	6 40 ± 1 17
C	19	141 1?5	11.53 ± 0 ?3	6 0? ± 0 58
D	8	1 6-210	11.29 ± 0.80	4.80 ± 0 9?

Several a imals were e luded due to inadequate mapping prior to the onset of ventricular t hycardia.
†HR = heart rate N-ST = number of lead with elevation of ST ΣST = sum of ST elevations in m ll olts.

Table III Incidence of ventricular arrhythmia

Group	*Ectopics*	*Tachycardia*	*Fibrillation*
Untreated group			
A (N = 16)	2	1	1
B (N = ?3)	9	5	4
C (N = 18)	?	?	4
D (N = 8)	0	0	0
Procainamide group			
A (N = 3)	3	1	0
B (N = 8)	8	4	0
C (N = 4)	4	2	0
D (N = ?)	2	2	1

have proportionate elevations of coronary blood flow in the preischemic period

With the advent of complete coronary occlu sion the transmural flow level is presumably reduced proportionately so that oxygen delivery per beat is similar Thus in a prior study of coronary blood flow using the Kr clearance technique we have observed coronary flow/100 Gm of left ventricle to decline from 0 67 ± 0 05 ml./beat to 0 23 ± 0 02 ml./beat at a mean sinus rate of 132 ± 12 that was not significantly changed during ischemia In a group with an initial heart rate of 165 ± 9 that was also essen tially unchanged by ischemia coronary flow per 100 Gm declined from 0 85 ± 0 06 ml /beat to 0 33 ± 0 02 ml /beat after occlusion of the ante rior descending artery [11]

Previous studies of acute heart rate change during ischemia involved occlusion by extrinsic compression of a coronary artery with external ligation or balloon which may affect neural inner vation of the ischemic tissue Although atropine induced sinus tachycardia was observed to increase the degree of ST segment elevation [15] the number of leads involved were not increased In a prior study using an open chest preparation a

recorded on a multi channel oscilloscope recorder * Complete coronary occlusion was evidenced by a sustained reduction of mean coronary pressure to approximately 25 mm Hg and the appearance of an injury potential on standard Lead 1 in all animals studied

During the initial 15 minutes of ischemia the rhythm was continuously monitored on the oscilloscope and recorded photographically Ectopic beats were considered significant if there were more than five per minute multifocal occurred in couplets, or demonstrated R on T phenomenon Animals who developed ventricular fibrillation within the first minute of occlusion were excluded due to the inability to record the relevant data from precordial ECG mapping The animals developing ventricular ectopic beats were assigned randomly into treatment and control groups For treatment procainamide was administered as a bolus of 10 mg /Kg intravenously at the onset of ventricular tachycardia defined as runs of three or more ectopic beats in succession

Based on the initial heart rate at intervals of 35 beats/minute animals were arbitrarily divided into four groups Group A was 70/minute to 105, Group B 106 to 140 beats Group C 141 to 175 beats Group D 175 to 210 beats Student s t test was applied to determine significance

Results

All animals maintained normal arterial pH and pO during the experiment Acute ischemia was induced in 82 animals who were divided into four categories on the bases of the spontaneous heart rate immediately prior to ischemia There was no significant change in the sinus rate or mean aortic pressure after infarction (Table I) except for a modest rate increase in Group A Thirty five dogs developed significant ventricular ectopic beats The N-ST and ΣST segment elevations did not differ significantly in the four groups of animals studied during the initial 15 minutes of ischemia (Table II) This suggested that by this technique the severity of ischemia was comparable in the four groups

Relation of ventricular ectopics to the resting heart rate There was a modest increase in the incidence of ventricular ectopics in the groups of animals with sinus tachycardia that was only significant in the 106 to 140 beat heart range (Fig 1), using chi square with a one tailed test Combining all the animals with rates greater than 100/min , 47 per cent of the latter were observed to develop ectopic beats compared to only 21 per cent in the group with the lower heart rate ($P < 0.05$) In Group D with the highest degree of sinus tachycardia, ventricular ectopics were seen less frequently than Groups B and C

The incidence of ventricular tachycardia was not significantly higher in Groups B and C versus Group A When the former two groups were combined for comparison with Group A the chi square test still fell short of significance ($P < 0.10 > 0.05$)

Antiarrhythmic response to procainamide Of the 35 dogs who developed ectopic beats 18 were untreated and served as controls Eleven of these animals developed ventricular tachycardia and nine progressed to ventricular fibrillation (Table III, Fig 2) In the 17 dogs comprising the treatment group, procainamide, 10 mg /Kg , was given as an intravenous bolus at the onset of ventricular tachycardia The incidence of ventricular fibrillation was diminished significantly to one out of nine ($P < 0.001$) The responders maintained sinus rhythm for the remainder of the observation period without a change in heart rate aortic pressure or the extent of injury as judged from precordial mapping

Discussion

Several prior studies have indicated an important effect of induced heart rate increments on the incidence of arrhythmias during experimental myocardial ischemia [1, 2] Since such increments uniformly evoked ventricular tachycardia in one of these studies [1] it was deemed important to assess the influence of spontaneous variation in sinus rhythm The variation of resting heart rate in these experimental animals is presumably intrinsic with a superimposed influence of anesthesia on neural input to the sinus node as well as direct effects on the latter structure Artificial respiration carotid arteriotomy catheter placement and duration of experiment may also have effects but all of these variables were similar in the four groups studied

Heart rate was constant for at least 30 minutes prior to coronary occlusion and in general the sinus rate remained unchanged in the ischemic period unless an arrhythmia supervened It is

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modest increase of ectopic beats in the group with a spontaneous sinus rate between 105 to 140 per minute there was no significant increase in ventricular tachycardia with ischemic heart rates up to 179 ± 5 9 This is consistent with experience in the unanesthetized dog

With rapid spontaneous heart rates above 175 beats/minute ventricular ectopia were unexpectedly less than in the intermediate range It is possible that in this group myocardial oxygen requirements may have been partially offset by a decreased end diastolic pressure and volume attending high rates Rapid heart rate may also produce an over drive effect tending to decrease the incidence of ventricular arrhythmias

Whether the ineffectiveness of procainamide in the study by Hope and associates is due to factors related to the animal model is not clear However in the intact anesthetized dog this agent has clearly been effective in the treatment of ventricular arrhythmias and pre existent heart rate does not appear to be a major determinant of efficacy This is consistent with the reduced incidence of ventricular fibrillation in man after the antiarrhythmic agent compared to acute infarction treated with placebo

Summary

Acute pacing induced tachycardia in early ischemia allegedly promotes ventricular arrhythmias which appear unresponsive to antiarrhythmic agents rasing question as to the efficacy of drug intervention clinically To determine whether spontaneous sinus rate has the same relationship to arrhythmia incidence and responsiveness in the intact anesthetized dog 82 animals were continuously monitored during a high risk arrhythmic period the initial 15 minutes of ischemia Proximal occlusion of the anterior descending artery was induced by inflating a balloon tipped catheter There was a modest increase in the incidence of VPB s at heart rates of 106 *to* 140 per minute compared to 70 to 105 beats which was not seen at higher heart rates However ventricular tachycardia was *not* correlated with the sinus rate over a range of 70 to 210 beats *per minute* To assess the relation of heart rate and responsiveness to antiarrhythmic agents a group of 17 dogs received procainamide 10 mg /Kg *intravenously* at the onset of ventricular tachycardia These were compared with an untreated group having similar heart rate levels and equivalent injury in terms of the number and sum of precordial leads with ST segment elevation Nine of the 18 untreated animals with VPB s progressed to fibrillation the incidence of fibrillation was reduced to one of 17 after procainamide ($P < 0.01$) Thus spontaneous heart rate over a broad range had no significant influence on the incidence of ventricular tachycardia during ischemia The latter is responsive to appropriate antiarrhythmic intervention apparently independent of initial heart rate

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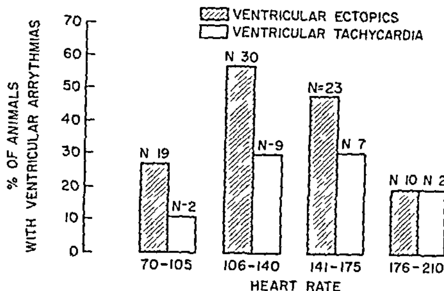


Fig 1 Incidence of ventricular ectopics and ventricular tachycardia at different sinus rates Group B animals ranging from 106 to 140 beats per minute had a significantly higher incidence of ventricular ectopics ($P < 0.05$) but none of the groups with faster heart rates had a significantly greater incidence of tachycardia

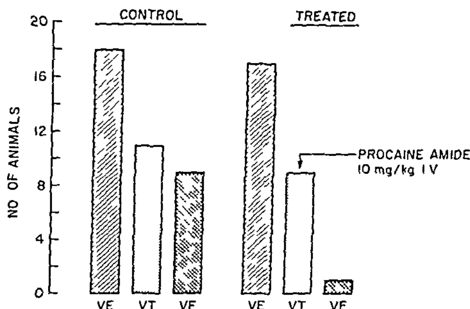


Fig 2 Response of ventricular arrhythmias to procainamide *VE* = ventricular ectopics *VT* = ventricular tachycardia *VF* = ventricular fibrillation There was a significantly lower incidence of ventricular fibrillation in the treated group ($P < 0.001$) Of eleven animals developing ventricular tachycardia nine fibrillated without treatment In the nine treated for ventricular tachycardia with procainamide only one fibrillated

substantial reduction of fibrillation threshold occurred when the sinus rate was enhanced more than threefold but there were no observations reported on spontaneous arrhythmias after the rate increment [16] In a similar model an enhanced incidence of arrhythmias was observed during pacing after coronary ligation in animals when the sinus rate was less than 80/minute or above 160/minute This study differed from our own in that there were few observations in the initial 15 minutes of ischemia In addition each animal was paced at varied rates for different period during the three hours of observation

During right atrial pacing in open chest animals a definite increase in incidence of ventricular tachycardia was uniformly observed with rates above 140/minute during early minutes of ischemia [1] Several factors may account for the contrast with our own observations In addition to the alteration of hemodynamics the open chest preparation may alter myocardial catechol amine stores [17] while pericardiectomy may affect arrhythmia incidence [18] Pacing of the heart may itself evoke release of catecholamines[1] which are known to be arrhythmogenic at suitable doses

Although this intact animal model did show a

Echocardiographic correlate of presystolic pulmonary ejection sound in congenital valvular pulmonic stenosis

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The ejection click of congenital valvular pulmonic stenosis has been used as an important diagnostic sign and a predictor of hemodynamic severity[1] The click occurs at the onset of right ventricular ejection and is thought to be due to abrupt tensing of pulmonic valve leaflets as they reach the limit of their excursion into the pulmonary artery Recently the influence of presystolic pressure events in the generation of the systolic ejection sound has been appreciated and diastolic opening or doming of the valve has been demonstrated[2] This report describes a patient with congenital valvular pulmonic stenosis in whom a consistent prosystolic ejection click was coincident with presystolic opening of the pulmonary valve by echocardiographic studies Additional hemodynamic measurements substantiated this observation

Case report

A 31 year-old man was discovered to have a heart murmur in infancy His growth and development were normal but during childhood his participation in strenuous games was limited by shortness of breath. During the several years prior to admission his effort tolerance was limited to one flight of stairs. Three years prior to admission he began to experience frequent episodes of dizziness unrelated to exertion and occasional palpitations but noted no temporal relationship between these symptoms.

Physical examination revealed a well developed moderately obese Caucasian male Blood pressure 110/80 in each arm pulse rate 70 per minute respiratory rate 14 per minute Jugular venous pulsations were visible 4 cm above the sternal angle and a prominent A wave was present. The apex impulse was palpated in the sixth left intercostal space 1 cm lateral to the midclavicular line A sustained systolic lift was present just lateral to the left sternal edge A systolic thrill was present in the second and third left intercostal spaces S1 was normal, S2 was single A Grade 4/6 harsh crescendo-decrescendo systolic murmur was heard maximally in the second and third left intercostal spaces and radiated down the left sternal edge A sharp presystolic sound interpreted as a prominent S4 gallop was heard along the left sternal edge (LSE) from the second to the fifth intercostal spaces. A systolic ejection click was not heard. Acrocyanosis of the fingers and toes was present.

The ECG revealed NSR with uniform VPCs right atrial enlargement, and right ventricular hypertrophy PA and lateral chest x ray revealed modest cardiomegaly (C/T ratio 0 5) and main pulmonary artery dilatation. Phonocardiography was performed with a Sanborn recorder Microphones were positioned in the second right and left interspaces, in the fourth LICS at the sternal edge and at the apex Heart sounds were recorded at high pass filter frequencies of 50 100, 200, and 400 Hz. Fig 1 is a phonocardiogram recorded in the second left intercostal space (PA) and at the apex at a filter frequency of 50 Hz. A presystolic ejection click (x) preceded an S4 gallop sound by some 20 msec. and the onset of QRS by 70 msec. It persisted through both phases of respiration Fig 2 was recorded in the same positions at a high pass filter frequency of 400 Hz. The high frequency character of the presystolic click is demonstrated by this recording Note that the lower pitched S4 gallop is no longer seen at this filter frequency

Echocardiograms of the pulmonic valve were obtained with a Unirad echocardiograph interfaced to a Tetronix strip chart recorder A phonocardiogram was simultaneously recorded in the third left interspace at a filter frequency of 100 Hz Fig 3 shows that the click (x) occurs precisely as the pulmonic valve completes its full opening movement before onset of ventricular systole

Cardiac catheterization revealed severe valvular pulmonic stenosis with a right ventricular systolic pressure of 110 mm Hg and a mean right atrial pressure of 5 mm Hg with an A wave of 1o mm. Hg The pulmonary artery pressure was 1?/5 mm Hg and an abrupt pressure gradient was demonstrated on a slow pull back at the level of the valve Cardiac index by the Fick method was 1 6 L./min /M and a right to left shunt was present at the atrial level with a Qs/Qp of 1 4 1 Right ventricular angiocardiography revealed a dome like pulmonic valve characteristic of congenital valvar pulmonic stenosis.

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Fig 3 Simultaneous pulmonic valve echocardiogram, reference ECG and phonocardiogram recorded at high pass filter frequency of 100 Hz in the third left intercostal space Ejection click (X) occurs in diastole coincident with pulmonic valve opening

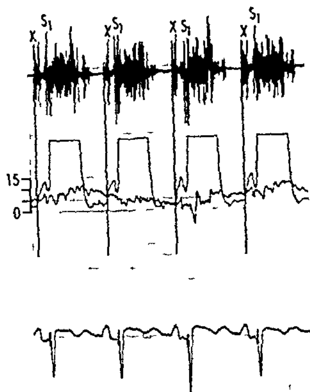


Fig 4 Simultaneous phonocardiogram (upper panel) superimposed pulmonary artery and right ventricular pressures (middle panel) and reference ECG (lower panel) recorded at operation Ejection click (X) occurs during diastole at the RV PA pressure crossover point

in response to atrial systole and found that diastolic valve excursion in inspiration was uniformly greater than in expiration These studies also confirmed that the presence and intensity of the systolic ejection click were dependent on the position of the valve leaflets at the onset of ventricular systole

Two cases of congenital valvular pulmonic stenosis with presystolic ejection clicks have been previously reported[2,3] In each of these cases simultaneous hemodynamic-phonocardiographic recordings demonstrated the click to occur at the point of diastolic RV PA pressure crossover The crossover point was usually in response to atrial systole but in the case reported by Hultgren and associates even earlier pressure crossover resulted in an early diastolic click In both patients presystolic valve doming was confirmed by angiocardiography Each of these patients had severe valvular stenosis In the case presented here the presystolic ejection click similarly occurred at an RV PA diastolic pressure crossover point and was timed with simultaneous pulmonic valve opening by echocardiography The latter method is more precise than cineangiography in correlative timing of valve motion with sound events In addition simultaneous physiologic parameters can be obtained on a strip chart recorder

It is probable that complete presystolic pulmonic valve opening is common in patients with severe congenital pulmonic stenosis This phenomenon reflects increased end diastolic pressure in the hypertrophied right ventricle Generation of a click by a suddenly tensed pulmonic valve requires rapid acceleration of the valve to the point of maximum excursion The occurrence of this sound in diastole reflects an unusually rapid rate of ventricular pressure rise in response to the volume imparted by RA systole and would seem to indicate a relatively less compliant right ventricle

Several physical signs have been emphasized as aids in differentiating mild to moderate from severe congenital valvular stenosis[4] A presystolic ejection click provides an additional useful clue to early opening of the pulmonic valve and indicates severe valvular obstruction As illustrated by this case the click may not be appreciated independently from a loud S4 gallop and simultaneous phonocardiographic-echocardiographic studies can be useful in determining the origin of the presystolic sounds

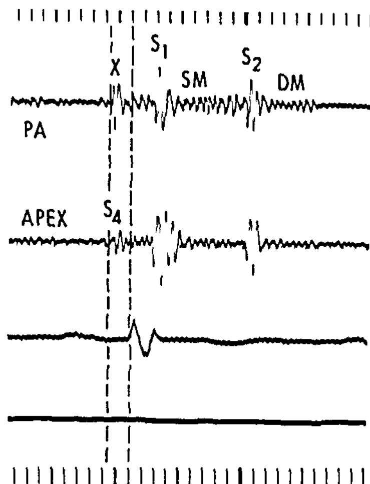


Fig 1 Phonocardiogram recorded at the second LICS at high pass filter frequency of 50 Hz *The first vertical line* illustrates that the ejection click *(X)* precedes onset of an S4 gallop by 20 msec *The second vertical line* indicates the onset of the QRS

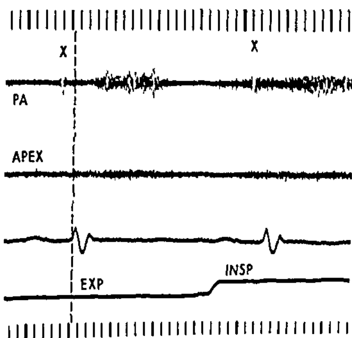


Fig 2 Phonocardiogram recorded at a high pass filter frequency of 400 Hz in left second ICS and at apex The high frequency ejection click *(X)* was recorded in inspiration *(INSP)* and expiration *(EXP)* *The vertical line* denotes the onset of QRS

The patient underwent pulmonic valvotomy and closure of a patent foramen ovale At the time of operation, right ventricular pressure pulmonary artery pressure and heart sounds were simultaneously recorded A Brush recorder was used and pressures were obtained by puncture of the RV and PA with 18 gauge needles The needles were connected to Statham P37B transducers by 24 inch lengths of saline filled tubing The upper record of Fig 4 is a phonocardiogram recorded at a high pass filter frequency of 200 Hz The middle record is a superimposition of right ventricular and pulmonary artery pressures The lower record is a reference electrocardiogram Paper speed was 50 mm /sec The ejection click (X) occurs when the RV pressure exceeds PA pressure In each instance the pressure crossover occurs prior to onset of ventricular systole and is effected by atrial systole This observation accounts for presystolic opening of the pulmonic valve associated with presystolic occurrence of the valvular click

Comment

Although the ejection click of congenital valvular pulmonic stenosis was first described some 75 years ago, the mechanism of its production has only recently been elucidated Both Reeve[3] and Hultgren and associates[2] performed simultaneous RV angiocardiography and phonocardiography and noted that the ejection click coincided with sudden halting of valve movement into the pulmonary artery at the onset of RV ejection This work emphasized the importance of valvular events in the genesis of an ejection click The importance of the diastolic RV PA pressure relationship in the generation of the click was demonstrated in studies of the characteristic respiratory variation of this sound[3] It was observed that during expiration PA pressure exceeded RV pressure at end diastole thus keeping the pulmonic valve in a closed position until onset of ventricular systole A click was then uniformly present in early ventricular systole as the valve domed upward During inspiration the augmented diastolic inflow sufficiently increased right ventricular diastolic pressure to levels greater than the PA diastolic pressure The valve opened in late diastole and no ejection click was noted in ventricular systole

The echocardiogram of a normal pulmonic valve was first reported by Gramiak and colleagues[4] They observed presystolic opening movement following deep inspiration in a normal subject

Weyman and co workers[5] reported echocardiographic confirmation of presystolic valve opening in congenital valvular pulmonic stenosis They demonstrated greater than normal valve motion

Valvular heart disease in osteogenesis imperfecta

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Osteogenesis imperfecta is included in the group of hereditary disorders of connective tissue which includes the Ehlers Danlos syndrome the Marfan syndrome *pseudoxanthoma elasticum* and the Hurler syndrome While cardiovascular involvement is associated with each of these disorders it is least common in *osteogenesis imperfecta* with less than 20 cases reported in the literature This report describes two patients with mitral valvular heart disease due to *osteogenesis imperfecta* a father and daughter who underwent cardiac catheterization and open heart surgery Included is the second reported patient with *osteogenesis imperfecta* to undergo successful mitral valve replacement

Case reports

Patient 1 A 55-year-old radio engineer with known *osteogenesis imperfecta* and a history of recurrent fractures was noted to have a heart murmur and mild hypertension on a routine insurance examination in 1969 and was referred for evaluation The patient was a short white male with multiple long bone deformities kyphosis a triangular shaped head and blue sclerae His blood pressure was 140/100 mm Hg and his fundi showed mild arteriolar narrowing The point of maximal cardiac impulse was in the fifth intercostal space 10 cm to the left of the midsternal line The first heart sound was diminished, the second heart sound was increased in intensity and there was a Grade II/VI apical pansystolic murmur which radiated to the axilla The electrocardiogram showed sinus rhythm and increased precordial QRS voltage The chest roentgenogram demonstrated a normal heart size a prominent aorta coarsened bony structures with diminished trabeculation and a compression fracture of the ninth thoracic vertebra (Fig 1)

From the Di isi n f Card ol gy D partm t of Medi in Uni ers ty of Oreg n H alth Scie es Ce te P rtland Ore

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Reprint requests Fra k E Kloste M D D isi n f C rd ol gy Un ers ty of Oreg H lth Scie ces C t 3181 S W Sam J kson Park Rd P rtl nd, Or 9 ?01

The patient underwent cardiac catheterization which showed mild mitral regurgitation and trivial aortic insufficiency Pressures were normal in all cardiac chambers and the cardiac output was normal at rest Coronary arteriograms showed insignificant disease of the left system and a normal right coronary artery Evaluation of his hyperten ion showed no secondary causes and he was discharged on antihyperten sive therapy

He remained asymptomatic with his hypertension well controlled until late 19 3 when he presented with increa ing congestive heart failure The electrocardiogram showed left ventricular hypertrophy with secondary ST T changes and cardiomegaly with left ventricular prominence was present on the chest roentgenogram (Fig 1) Echocardiography demonstrated left atrial and left ventricular enlargement normal mitral valve motion with no evidence of systolic prolapse and a normal aortic valve At repeat cardiac catheterization pressures were right atrial mean 2 mm Hg pulmonary artery 3?/15 mm. Hg (mean ?4 mm Hg) pulmonary wedge A wave 14 mm Hg, V wave 36 mm Hg (mean 17 mm Hg) left ventricle 13?/18 mm. Hg brachial artery 140/?0 mm. Hg (mean 9? mm Hg) There was no dia tolic pressure gradient between pulmonary wedge and left ventricle and there was no systolic pressure gradient between left ventricle and brachial artery The arteriovenous oxygen difference was 4 9 vol per cent and the Fick cardiac output was 5 5 L./min (3.1 L./min / M) at rest

A left ventricular cineangiogram demonstrated marked mitral regurgitation with symmetrical systolic wall motion except for mild apical hypokinesis (Fig 2) The end-diastolic volume index was 183 ml /M the end-systolic volume index was 60 ml./M and the ejection fraction was 0 6 There was no mitral or aortic valve calcification Supravalvular aortography again demonstrated trivial aortic insufficiency a tricuspid aortic valve and no dilatation of the aortic root Coronary arteriograms showed a significant stenosis in the proximal left anterior descending coronary artery and multiple stenoses in the midportion and distal left circumflex The right coronary artery was dominant with minimal disease

At surgery left ventricular hypertrophy and left atrial enlargement were noted with no evidence of previous myocardial infarction The aortic root was not dilated and the aortic valve cusps were not examined The mitral annulus was dilated and there was distortion of the architecture of the mitral leaflets with severe mitral regurgitation No commissural fusion was present The valve was replaced with a Starr Edwards 63?0 *mitral* valve prosthesis. Attempts were made to bypass the stenosis in the left anterior descending artery with

Summary

A presystolic ejection click was present in a patient with congenital valvular pulmonic stenosis The coincidence of this sound with presystolic pulmonary valve opening was demonstrated by simultaneous phonoechocardiography Hemodynamic confirmation of this observation was made by demonstrating presystolic crossover of RV-PA pressures

This sound was distinguished on phonocardiogram as a high frequency sound separate from a lower frequency presystolic (S4) gallop

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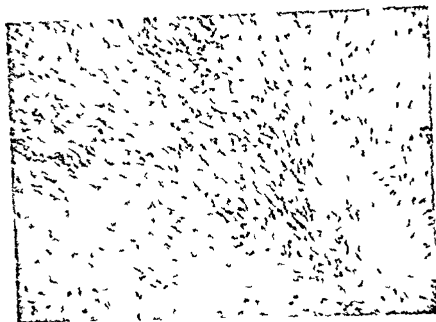


Fig. 3. Microscopic section of the mitral valve in Patient 1 demonstrating a central area of myxoid degeneration surrounded by normal valvular tissue. (Hematoxylin and eosin stain; original magnification ×155.)

peripheral arterial pulses were bounding. The point of maximal cardiac impulse was active and diffuse in the sixth intercostal space at the anterior axillary line. The first and second heart sounds were diminished. A Grade II/VI immediate high-pitched diastolic decrescendo murmur along the upper left sternal border and a Grade II/VI systolic ejection murmur which radiated to the carotids were heard. There was a Grade II/VI holosystolic musical murmur at the apex which radiated to the axilla and the lower left sternal border, and a Grade II/VI mid-diastolic rumble without presystolic accentuation or an opening snap. The electrocardiogram showed sinus rhythm and left ventricular hypertrophy. Left ventricular, right ventricular, and left atrial enlargement were present on the chest roentgenogram.

At cardiac catheterization,* pressures were: right atrial mean 9 mm Hg; pulmonary artery 65/30 mm Hg (mean 42 mm Hg); pulmonary wedge A wave 20 mm Hg, V wave 50 mm Hg (mean 22 mm Hg); left ventricle 140/22 mm Hg; aorta 140/60 mm Hg (mean 85 mm Hg). Simultaneous left ventricle and pulmonary capillary wedge pressure recordings showed no diastolic pressure gradient and there was no systolic gradient on pullback from the left ventricle to aorta. The Fick cardiac output was 4.7 L/min (2.8 L/min/M²) at rest with an arteriovenous oxygen difference of 5.1 vol. per cent. A left ventricular cineangiogram showed a dilated left ventricle and severe mitral regurgitation. A supravalvular aortic cineangiogram showed marked aortic insufficiency with no aortic valve calcification.

When examined at surgery,† all three aortic leaflets were elongated and prolapsed. There was rupture of the chordal structures of the anterior leaflet of the mitral valve. Double valve replacement was performed with Smeloff-Cutter mitral and aortic prostheses. Immediately postoperatively, the patient developed a low cardiac output state with hypotension and congestive heart failure complicated by metabolic acidosis. She died during the first postoperative day. Autopsy showed massive subendocardial infarction of the left ventricle and marked thinning of the aortic wall but no cystic myxoid degeneration.

*Performed at Providence Hospital, Portland, Oregon.
†Performed at Emanuel Hospital, Portland, Oregon.

Table I. Reported cases of valvular heart disease in osteogenesis imperfecta

	Aortic insufficiency	*Mitral insufficiency*	*Aortic and mitral insufficiency*
McKusick	2	0	4
Criscitiello	2	0	1
Browell	1	0	0
Heckman	0	1	0
Carey	1	0	0
Heppner*	1	0	0
Wood	0	2	0
Weisinger*	2	0	0
Stein	0	1	1
Total	9	4	6

Discussion

Cardiovascular abnormalities have been described in all of the heritable disorders of connective tissue.[1] With regard to aortic and mitral valve involvement and microscopic connective tissue findings, these abnormalities are most similar in osteogenesis imperfecta and the Marfan syn-

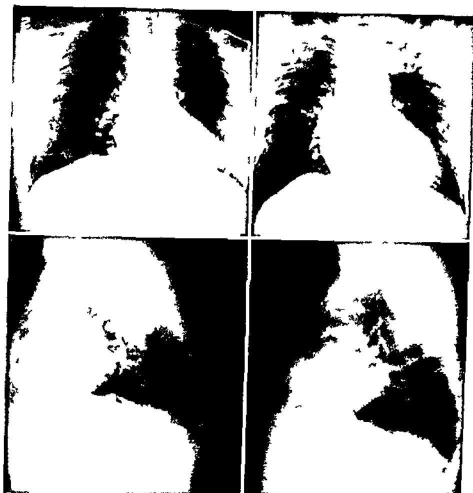


Fig 1 Chest roentgenograms in Patient 1 showing normal heart size in 1969 (*left panels*) and cardiomegaly with pulmonary vascular congestion two weeks prior to operation in 1973 (*right panels*)



Fig 2 Left ventricular cineangiogram in the right anterior oblique position in Patient 1 The end diastolic (*left*) and end systolic images demonstrate a normal ejection fraction (0 67) with marked mitral regurgitation and an enlarged left atrium

a vein graft but the middle portion of the vessel was intramyocardial and the distal vessel was too tortuous and small Pathological examination of the mitral valve demonstrated severe myxoid degeneration (Fig 3) Postoperatively his course was uneventful and he was discharged taking digoxin and Coumadin He is now 32 months postoperative and in Functional Class I (NYHA)

Patient 2 A 26-year old housewife the daughter of Patient 1 had known *osteogenesis imperfecta* since childhood complicated by multiple fractures occurring almost yearly Over an 8-month period she noted increasing fatigue decreasing exercise tolerance and progressive dyspnea with exertion Two months prior to cardiac catheterization she developed orthopnea and paroxysmal nocturnal dyspnea and was treated with digitalis and diuretics with some improvement Her past history was negative for rheumatic fever scarlet fever chest trauma hypertension or diabetes mellitus

The patient was a slightly obese female with severe orthopedic deformities Her head was triangular in shape and her sclerae were blue The blood pressure was 170/50 and

culties occurred in our patients or in those reported by Wysinger[8] and it is uncertain whether this will be a frequent complication

Summary

Aortic and mitral valve abnormalities have been reported which clearly appear to be related to the underlying connective tissue disorder in two patients a father and daughter with *osteogenesis imperfecta* Although this appears to occur with a much lower prevalence and lesser severity than in the Marfan syndrome the true prevalence of cardiac connective tissue involvement is not known and the orthopedic complications of *osteogenesis imperfecta* may have overshadowed attention to cardiovascular abnormalities In evaluating patients with *osteogenesis imperfecta* careful attention should be paid to cardiovascular findings and if valvular lesions are noted patients should be instructed regarding the need for antibiotic prophylaxis for dental and surgical procedures The valvular lesions can progress and regular follow up cardiovascular evaluation should be planned Finally despite potential problems with tissue friability and healing and a possible tendency for increased bleeding successful valve replacement can be carried out if necessitated by cardiac disability

We gratefully acknowledge Dr Rodney L. Crislip s generosity in providing data concerning Patient [illegible]

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drome However, although the prevalence of *osteogenesis imperfecta* and the Marfan syndrome in the general population are similar (one per 40,000 to one per 60 000)[1] clinically recognized cardiac abnormalities are common in the Marfan syndrome but have been reported infrequently in *osteogenesis imperfecta* Patients described in the medical literature with aortic and/or mitral valve disease apparently related to underlying *osteogenesis imperfecta* are summarized in Table I The majority of these were diagnosed clinically and did not have hemodynamic or angiographic evaluation Earlier authors have attributed cardiac findings to rheumatic disease or apparently unrelated congenital heart lesions,[3, 9] and it seems likely that other patients with *osteogenesis imperfecta* and related cardiac disease have been assumed to have rheumatic or atherosclerotic cardiovascular etiologies

Despite the uncertainty about etiology in some patients the marked disparity in clinically obvious cardiac involvement between *osteogenesis imperfecta* and the Marfan syndrome appears real Browell and Drake[3] reviewed the records of the 24 patients with *osteogenesis imperfecta* examined at the Henry Ford Hospital between 1939 and 1965 and found only one patient with clinical evidence of heart disease In a similar review of New York Hospital records from 1932 through 1966 Heckman and Steinberg[4] found one case of mitral regurgitation in the 43 patients seen with *osteogenesis imperfecta* This probably reflects the wide range of expressivity of osteogenesis as observed by McKusick[1] and less severe involvement of the connective tissue of the aorta and aortic and mitral valve cusps Reports of microscopic anatomic findings are sparse[8, 9] and more complete postmortem studies may demonstrate more common involvement of cardiac connective tissues In addition a recent echocardiographic study demonstrated much more frequent cardiac involvement in the Marfan syndrome by this non invasive technique than had been recognized clinically[10] and it is possible that echographic studies in patients with *osteogenesis imperfecta* will demonstrate a similar high incidence of clinically inapparent involvement

Aortic insufficiency has been the most common cardiac lesion by clinical examination in *osteogenesis imperfecta*, with mitral insufficiency or involvement of both aortic and mitral valves occurring less often However, some individuals with single valve involvement clinically have been found at surgery or postmortem examination to have definite abnormalities of the other valve, as did Patient 1 in this study, further suggesting that more critical noninvasive or angiographic studies may demonstrate more extensive cardiac involvement than has been suspected by clinical examination Typical gross anatomic findings have included dilatation of the aortic root thinning elongation and sagging of the aortic valve cusps dilatation of the mitral valve ring, and redundance of the mitral leaflet with attenuation elongation and sometimes rupture of chordae tendineae[8] Fusion scarring or retraction of valve cusps have been present only after superimposed endocarditis Microscopic examination has demonstrated thinning of the aortic wall aortic valve cusps and mitral leaflets with a marked decrease in fibrous connective tissue and with cystic mucoid or myxoid degeneration[8, 9] Both the gross and microscopic findings are very similar to those seen in the Marfan syndrome

Surgical correction of valve abnormalities has been infrequent Prior to this report one successful mitral valve replacement and one mitral valve repair have been reported and successful aortic valve replacement has been described in two patients[8] This may again reflect the relative infrequency of severe valvular involvement, but may be related in part to limited exercise tolerance or capability in patients with osteogenesis due to orthopedic disability from multiple fractures or avoidance of activity which might incur fractures It has been anticipated that patients with osteogenesis might present the same difficulty in securing sutures and subsequent healing that has been encountered in those with the Marfan syndrome and surgical reports have described friability of tissues[7, 8] However with careful placement and buttressing of sutures serious postoperative mechanical problems have been avoided In addition patients with osteogenesis have demonstrated ill defined bleeding tendencies[1] and postoperative bleeding problems did occur in the patients reported by Criscitiello and associates and by Wood and co authors[7] No bleeding diffi

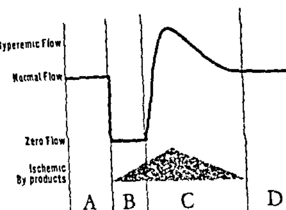


Fig 1 Reactive hyperemia in the dog Normal coronary artery flow *(A)* is converted to zero *(B)* by a short coronary occlusion The ensuing ischemia causes a buildup of vasoactive products. Reactive hyperemia *(C)* follows release of the occlusion Flow then subsides to normal *(D)* as byproducts of ischemic metabolism are dissipated

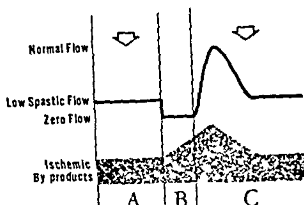


Fig 2 During experimental AMI low spastic flow (A) due to injury vasospasm (arrow) results in insufficient ischemia to reverse spasm A short coronary occlusion *(B)* increases the level of ischemia (and the attendant vasoactive metabolite) sufficiently to reverse spasm temporarily (C) Note that overshoot—reactive hyperemia—is absent in some animals it was present but attenuated A flow probe effect prevented visualization of rapid return of spasm as depicted in *(C)*

that transient coronary artery spasm occurs more frequently than commonly recognized and possibly is present early in the course of incipient AMI Coronary atherosclerosis is prominent in type A personalities and vascular injury by repeated episodes of spasm might accelerate the development of atherosclerosis

Reperfusion models in AMI

Recently because of the need to evaluate coronary bypass surgery in evolving AMI reperfusion experiments in dogs were performed In this model the coronary occlusion is released after creation of the infarct

Although different in purpose these experiments are similar in basic design and result to the study which prompted the injury vasospasm hypothesis The recent studies are also interpreted by this observer as showing apparent intramyocardial vasospasm and they appear to provide additional evidence for injury vasospasm There was reduced reperfusion flow and attenuated reactive hyperemia The combined series of reperfusion experiments demonstrate that reperfusion flow reduces progressively and this is interpreted as reflecting increasingly severe spasm paralleling the evolution of myocardial necrosis At 15 minutes flow was variable and at 2 hours it was 34 per cent at 4 hours 23% and at 4 to 7 days usually less than 3 per cent of control values Electromagnetic flow probes used in some studies should be treated with caution as they can inhibit the development of spasm

Appropriately there is growing interest in experimental models in AMI The reperfusion model appears to be valuable for the general study of AMI as excepting for the absence of stenotic atherosclerosis it probably simulates events *during* clinical AMI Practically all previous experimental studies of AMI including recently conducted investigations used permanent coronary occlusions and such models appear improper except for the study of embolization and secondary thrombosis Experimental models appropriate to study the *development of* AMI in man do not exist as it is difficult to create a model which resembles both the emotional and coronary artery status of man

Vasospasm and the autonomic nervous system

Alterations in the autonomic nervous system secondary to emotional stress probably are a significant cause of coronary spasm in IHD However spasm is indicated only rarely as the final common pathway for emotional tension For AMI this probably is because of the ascendency of the view that this disorder is due directly to stenotic coronary artery disease Stress might cause AMI by an inappropriate autonomic vasomotor response with vasoconstriction replacing vasodilation there is evidence that stress may result in a parasympathetic rather than an appropriate sympathetic response The importance of

The injury-vasospasm hypothesis of ischemic heart disease, revisited

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Interest in coronary artery vasospasm in ischemic heart disease (IHD) while growing, is limited mainly to variant angina pectoris (AP)[1-4] The injury vasospasm hypothesis[5] gives spasm a central role in IHD and was discussed recently in this JOURNAL in regard to therapeutic possibilities in acute myocardial infarction (AMI)

In order to foster the current interest in vasospasm this essay will review the general hypothesis and its experimental basis, and update it by interpreting findings in the recent literature in context to spasm Also, it will be emphasized that vasospasm should be considered in relation to the autoregulation of coronary artery blood flow

The injury vasospasm hypothesis of IHD

The hypothesis is based on a study[7] where reduced apparently spastic coronary artery blood flow was found during the course of experimental AMI This spasm is attributed to an injury reaction to necrotic muscle In addition to spasm being present during AMI, spasm also is considered to initiate attacks of chest pain causing either AP or AMI This latter spasm is related to chronic ischemic myocardial damage secondary to stenotic coronary artery disease and is designated as reflex spasm to indicate its probable mode of origin In the initiation of spasm emotional and unknown factors probably are important especially in cases without significant atherosclerosis

Vasospasm and coronary artery autoregulation

Spasm probably represents failure of coronary artery autoregulation Normally spasm should not occur, and if for some reason it does should be reversed promptly Spasm causes myocardial ischemia and ischemia via the anoxic feedback mechanism of coronary artery autoregulation initiates prompt vasodilation Reactive hyperemia due to hypoxia probably is caused by the production of some vasodilator metabolite which accumulates in extracellular spaces during the period of ischemia (Fig 1)

The interplay between spasm and the anoxic feedback mechanism probably is of fundamental importance in understanding events in IHD and this interaction can be observed during the course of experimental AMI[7] Here injury vasospasm might be considered as resetting the anoxic feedback mechanism to a low and inappropriate level of flow However the autoregulatory mechanism can be manipulated to correct spasm temporarily In fact the ability to alternate between low and normal flow in experimental AMI[7] prompted the view that a reversible vascular condition i e vasospasm was present Low flow could be abolished by a short coronary occlusion and this is attributed to the accumulation of sufficient vasodilative material to overcome spasm (Fig 2) The typical hyperemic overshoot was attenuated and this as well as the reversal of low flow by ischemia provides evidence for the involvement of the autoregulatory mechanism by spasm

A clinical correlate of this reversal of spasm might be the occasional example of AP which is improved rather than worsened by exertion[11] Here physical effort causes sufficient hypoxia to actuate the anoxic feedback mechanism which then reverses (or prevents) the reflex spasm of AP

The induction of AMI also can be described in relation to the anoxic feedback mechanism (Fig 3) Demonstrable coronary artery spasm and electrocardiographic changes of ischemia can occur without chest pain and it is possible

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probably are extensions from small intramyocardial vessels. Spasm which is present during AMI as a direct injury reaction to necroctic muscle probably is limited to small mural arteries as most likely it is milder than the paroxysms which initiate AP and AMI. During the course of experimental AMI[7] spasm was not observed in epicardial arteries.

Coronary artery thrombosis in AMI

The injury vasospasm hypothesis attributes coronary artery thrombosis (CAT) to arterial stasis secondary to spasm and probably represents the first consideration of stasis in the pathogenesis of secondary CAT.

An additional and probably important factor might be spasm acting directly on epicardial vessels. Plaque rupture and/or hemorrhage commonly are associated with CAT and plaque rupture with subsequent thrombosis has been ascribed to spasm. Plaque rupture has been attributed to a vector force acting on the arterial wall[5] a view consistent to this observer with a bout of severe reflex spasm. It is of interest that the major proponents of plaque rupture leading to CAT do not support a vasospastic origin of these lesions.

The reported frequency of CAT with AMI varies widely and reports of high incidences might not be evidence that CAT are primary. The exact frequency probably never will be known as surviving cases of AMI are likely to be milder and be complicated less frequently by CAT than those with fatal transmural infarction. Perhaps only about 25 per cent of all cases of AMI have associated CAT.

Sudden coronary death and vasospasm

Vasospasm usually is not discussed as a possible cause of sudden coronary death (SCD) and was not mentioned in a recent large symposium on this subject. However in 1934 Leary attributed SCD to spasm causing plaque rupture and CAT. The lack of interest in spasm probably is because SCD might be similar to or identical with AMI and spasm is not emphasized in the latter disorder. In fact relatively recent symposia on AMI also have been devoid of comments about spasm.

There are several evidences that equate SCD to AMI and these can be used to indict a vasospastic origin of both conditions. Both have acute changes in epicardial coronary arteries myocardial microlesions and similar prodromata. Disrupted plaques which appear to be evidence for spasm have been found in one series of SCD in about half of the cases.[3] Further hemorrhages into subintimal plaques (which are often associated with plaque fracture[11]) were present almost universally in a study of SCD and were absent in control cases[7] and probably are evidence of recent paroxysms of spasm.

In SCD microlesions of myocardial necrosis are frequent and in early AMI necrotic microlesions have been found in otherwise normal muscle near the infarct and occasionally in distant myocardium. These lesions appear to be unexplained but might be morphologic stigmata of the prodromata of SCD and AMI and represent ischemic foci following subliminal bouts of spasm. The dyspnea which is part of the prodromata syndrome might be explained by mild injury vasospasm which causes impaired myocardial contractility. These microlesions may be involved in a vicious cycle of progressive myocardial injury and once overt necrosis develops the likelihood of a severe and possibly fatal attack of spasm increases. Such a possibility emphasizes the need to recognize and treat prodromata perhaps with currently available vasodilators. Treatment for several weeks might permit these lesions to heal and reduce the chance for a cardiac catastrophe. Long term therapy to prevent AMI might require agents other than vasodilators.

Myocarditis and AMI

Recently Woods Nimmo and Mackay Scollay[4] suggested that viruses can precipitate AMI in susceptible subjects a concept in keeping with the injury vasospasm hypothesis. These investigators found that 9 per cent of their series of AMI were associated with active Coxsackie infection a virus which causes significant myocardial injury. As 70 per cent of these cases were between 45 and 64 years of age and 19 of the 20 were males the virus probably acted synergistically with the usual causes of AMI. Soyannwo recently attributed a healed AMI to granulomatous myocarditis in a Nigerian with no coronary artery disease.

Myocarditis frequently mimics AMI[5] and it is possible that whether or not AMI develops

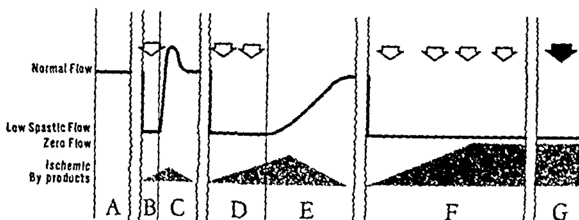


Fig 3 Preinfarct AP and AMI. Normal blood flow *(A)* is converted to low spastic flow *(B)* by a paroxysm of spasm (clear arrow). Spasm is reversed quickly *(C)* by reactive hyperemia. With a second attack of spasm *(D)* partial failure of the anoxic feedback mechanism results in continuation of spasm until sufficient vasodilative products accumulate to reverse spasm *(E)*. Note that recovery is slow and no reactive hyperemic flow is depicted. With a third episode of spasm *(F)* there is complete failure of the autoregulatory system and spasm continues until fresh myocardial injury (black arrow) develops which perpetuates the spasm and results in AMI *(G)*.

the autonomic system in IHD is emphasized by the induction of spasm in AP by parasympatheticomimetic agents and by evidence for alpha adrenergic receptor mediation of spasm. AMI has been described as a largely self induced breakdown in health consequent to stress and tension and the key failure might be the autoregulatory system subsequent to increasingly severe spasm.

Severity of coronary artery disease and IHD

There is a lack of constancy between the severity of coronary artery disease and the occurrence of IHD. This suggests an underlying rather than a direct role for atherosclerosis in initiating attacks of AMI and AP and permits consideration of reflex spasm.

Even effort (stable) AP probably is due to spasm as a quantitative relation between it and coronary disease does not obtain. Three vessel disease severe enough to cause cardiomyopathy can occur without angina and it is common to find prominent coronary atherosclerosis at autopsy without a history of angina. The severity and distribution of coronary disease is reported to be the same with stable severe, stable moderate and unstable AP. Similar degrees of coronary artery involvement can result in either AP or AMI with congestive heart failure.

Attacks of chest pain in effort AP are considered to be due to reflex injury vasospasm. With exertion relative ischemia develops which triggers an inappropriate injury reaction. As spasm continues byproducts of ischemia build up until the anoxic feedback mechanism is activated, which then reverses spasm. A major factor in favor of spasm is the efficacy of nitroglycerin.

Variant AP while commonly associated with single artery disease may have multiple vessel involvement or no atherosclerosis. Yet, cases with normal coronary arteries could not be distinguished clinically or by electrocardiograms from those with severe obstructive lesions. Also AMI can occur with mild or no atherosclerosis.

Thus with severe coronary artery disease there may be no attacks of reflex spasm or episodes may be expressed as AMI or AP of the stable, unstable or variant types. Conversely AMI and variant AP can occur with varying degrees of coronary disease. This diversity of responses emphasizes that it is unlikely that atherosclerosis *per se* precipitates chest pain in IHD.

Coronary artery spasm—epicardial and/or intramyocardial?

In considering spasm it appears important to place its site of origin and extent of involvement. While the autoregulation of coronary flow is located in small mural arteries, spasm is demonstrated by angiography in epicardial vessels. Some of the spasm seen during angiography has been attributed to catheter irritation and this recognition of one type of coronary injury-vasospasm might be propitious. Spontaneous paroxysms of spasm in large arterie

Addendum

It might be helpful to restate the injury-vasospasm hypothesis in light of a dual system of coronary artery regulation. This orientation attempts to unify the concept and also provides a more direct role for spasm of epicardial arteries. A dual regulatory system has been proposed for the brain[?] with intraparenchymal arteries under local metabolic control and extraparenchymal arteries under sympathetic influence. For the heart the equivalent to this is the anoxic-feedback mechanism which controls mural arteries and the autonomic nervous system which by means of the cardiac neural plexuses innervates epicardial arteries.

The two major causes of coronary spasm can be related to these dual controls and their associated vessels by the following groupings: myocardial injury/anoxic-feedback mechanism/mural spasm and emotional stress/autonomic nervous system/epicardial spasm. These groupings provide a concise summary and appear generally valid but it is likely that spasm from either system can involve both small and large coronary arteries. Emotional stress could induce spasm in small arteries as the cardiac plexuses innervate mural as well as epicardial arteries. Also spasm from myocardial injury probably extends to large arteries by a sensory reflex. If dual coronary artery regulation obtains it is reasonable that these systems are interconnected for cooperative flow control and there are sensory fibers which connect small mural arteries (and the myocardium) to the cardiac neural plexuses.

A second reason to support the probability of neural reflexes is the likelihood that such a reflex is involved in reversing spasm in epicardial arteries. The injury-vasospasm hypothesis attributes correction of spasm to the anoxic-feedback mechanism (Fig. 3) as this is the primary method for dilating coronary arteries in the face of myocardial ischemia. However this system is based in small mural arteries and a neural connection seems necessary for this mechanism to effect reversal of epicardial spasm. The conventional view is that coronary artery spasm is limited to epicardial arteries and that the small arteries are widely dilated in response to myocardial ischemia.

During the course of AMI injury-spasm is considered to occur and the limitation of this spasm to small mural arteries might be considered to militate against the reflex spread of spasm. However this spasm probably is milder than the paroxysms which initiate AP and AMI and the autonomic nervous system has been able to counter any reflex propagation of the injury-spasm. The general emphasis on neural mediation of coronary artery spasm in ischemic heart disease does not rule out a role for agents as prostaglandins.[?]

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crushing chest pain in myocarditis is due to *injury vasospasm*

That AMI can occur with primary myocardial injury is supported by the recent report[17] of a series of 12 cases of toxic cardiomyopathy without coronary obstruction which were complicated by AMI

Exercise AMI and AP

While regimes of exercise reduce the incidence of AMI[2] there are numerous instances of AMI occurring during programs designed to ward off this catastrophic event This apparent paradox might be explained in terms of the autoregulation of coronary artery blood flow It is suggested that exercise trains this system to respond properly and efficiently just as exertion improves the function of the other components of the cardio vascular system Thus with exercise the coronary vasculature responds promptly to relative ischemia by vasodilation

SCD and AMI occurring during exercise may represent an inappropriate and vasospastic response to ischemia Properly and on the basis of common sense it is commonly suggested that exercise in the middle aged and after AMI should be graded not scheduled tightly, or performed during periods of emotional stress

AP can be improved by exercise[19] and this might be due to a regularization of the autoregulatory mechanism The relative ischemia induced by graded exercise results in an appropriate vasodilative response Other factors as increased efficiency of cardiac action probably also are operative but if spasm initiates AP the autoregulatory mechanism has prime importance

Coronary artery bypass and developing AMI

The value of coronary artery bypass in improving myocardial blood flow in selected cases of IHD is well established Recently, this procedure has been performed within the first few hours of AMI[13,14] apparently because the acute attack of AMI is considered to be due directly to mechanical vascular occlusion

However, if the immediate cause of AMI is spasm the limiting factor to restoring blood flow to the level prior to the AMI is not atherosclerosis Coronary artery bypass surgery might be considered in the light that coronary artery disease is the underlying but not proximal cause of most cases of AMI Detection of the minority of cases of AMI with plaque rupture and/or thrombosis, where surgery might offer some benefit probably would be difficult

The future

It is possible that there now is sufficient interest in coronary artery spasm that its role in the various forms of IHD will be defined by appropriate experimental and clinical studies This goal has been proposed[5] and a hopeful sign has been the recent suggestion[9] that the elucidation of spasm might be important in understanding unstable AP, AMI, SCD, and AP with normal angiograms However the previous—and current—reluctance to consider vasospasm should be kept in mind The continuing general acceptance[11] that AMI is due to atherosclerotic coronary occlusion is not conducive to the development of alternate concepts as spasm

Definition of the part spasm plays in AMI and SCD appears particularly important because of immediate therapeutic implications[8] The older information that sympathectomy and stellate ganglion blockade improve AP[5] may renew interest in these modalities in IHD It is likely that the establishment of an important role for spasm will re emphasize that IHD is a clinical spectrum An interesting possibility might be the redefinition of IHD to emphasize a spastic origin of ischemia

Summary

The injury vasospasm hypothesis of IHD was discussed in relation to coronary artery autoregulation and the anoxic feedback mechanism Observations in the recent literature not usually attributed to spasm were examined in light of this phenomenon This includes reperfusion models of experimental AMI, the association of AMI with myocarditis and findings in AMI and SCD as necrotic microlesions prodromata and epicardial arterial plaque rupture and hemorrhage The disparity between the severity of coronary disease and the occurrence of the various types of IHD suggest that atherosclerosis itself does not precipitate attacks of chest pain It was emphasized that plaque rupture due to spasm might help induce CAT With exercise the possible importance of the autoregulatory system was explored in the prevention and induction of AMI and SCD and the improvement of AP

The role of spasm in IHD should be defined

The importance of magnesium deficiency in cardiovascular disease

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The role of magnesium in cardiovascular disease is not fully known primarily because magnesium measurements in patients have not been regularly obtained Physicians fail to appreciate the importance of this element in biology and medicine Although a spectroscopic method for rapid extremely accurate determination of small amounts of magnesium in body fluids has been available for many years magnesium data are lacking The more recent introduction of atomic absorption spectroscopy has facilitated the study of this major cation in the human body

A normal metabolism requires proper amounts of available magnesium and previous studies from our laboratory have revealed magnesium to be an extremely kinetic element in man Although magnesium is vital to the proper metabolic function of all cells of man the brief discussion to follow deals principally with selected aspects of magnesium deficiency in cardiac disease

Distribution of magnesium

The role of magnesium in metabolism has been well summarized recently[3] Magnesium is the fourth most plentiful cation in the body (approximately 2 000 mEq in a 70 kilogram man) following calcium (60 000 mEq) sodium (5 500 mEq) and potassium (3 000 mEq) Approximately 50 per cent of body magnesium is in bone and is not readily available as a dynamic reservoir for use in other body tissues Like potassium only a small part (1 per cent) of magnesium is in the extracellular fluid compartment The largest amount of magnesium which is active in magnesiokinetics is within the cells of the body in a concentration of about 28 mEq per liter Normally serum magnesium values are between 1 6 and 2 0 mEq per liter

Cardiac muscle has a high concentration of magnesium (17 4 to 19 8 mEq /liter) A higher concentration of magnesium is found in the ventricles than in the atria of the dog[5] There are no significant differences between magnesium concentrations in the right and left ventricles or the interventricular septum[6]

One third of the 20 to 25 mEq of magnesium present in a normal diet is absorbed in the small intestine[3] the remainder being excreted in the feces

Absorbed magnesium is excreted primarily by the kidney the amount excreted in the stool over two to three days being less than 1 4 per cent of the amount given[2] A diagram indicating the daily body turnover of magnesium in a female is shown in Fig 1 Studies with Mg revealed that the rate of excretion through the urine falls during the first 15 to 20 hours and then remains relatively stable up to 70 hours The cumulative excretion of Mg in the urine was as high as 10 7 per cent of the administered amount during the 70 hour observation period (Fig 2) The kidney is capable of reducing renal magnesium loss to less than 1 mEq per day when intake is nil[3] Aldosterone increases the renal excretion of magnesium whereas parathormone reduces excretion Also parathyroid hormone regulates in part both calcium and magnesium excretion and metabolism An increase in the blood magnesium cation reduces parathormone secretion and vice versa

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Magnesium in large doses can produce general anesthesia

Myocardial disease in experimentally produced magnesium deficiency

The effect of magnesium deficiency on the heart has been studied most extensively in the rat In 1936 Greenberg and associates[a] described myocardial degeneration with fibrosis and polymorphonuclear blastic infiltration in rats that were fed a low magnesium diet from birth[b] Lowenhaupt Schulman and Greenberg described in detail the basic histologic lesions of magnesium deficiency in the rat They noted distinct inflammatory and necrotic focal areas around small blood vessels In the acute stage the lesions were characterized by a collection of inflammatory cells with some areas progressing to necrosis and later scar formation Ko Fellers and Craig on the other hand attached little significance to relatively few focal degenerative changes occurring in the hearts of magnesium deficient rats ✓

Heggtviet Herman and Mishra[c] studied myocardial lesions of magnesium deficient rats using both light and electron microscopy After 14 days of magnesium depletion gross myocardial lesions ranging from small pale yellowish grey patches to large zones of necrosis and calcification were seen in 50 per cent of experimental animals Light microscopy revealed focal areas of necrosis and exudative inflammation in most magnesium deficient rats after 10 days particularly in subendocardial regions Muscle fibers adjacent to areas of necrosis showed increased sarcoplasmic eosinophilia patchy loss of cross striations vacuolization and accumulation of periodic acid Schiff (PAS) positive material Calcification in the granulomatous lesions was seen in approximately one half of the animals Progression of the lesions to scarring was also observed

Electron microscopic evidence of myocardial damage was seen early (after five days on a magnesium deficient diet) The mitochondria exhibited the earliest changes consisting of swelling and vacuolization compression and distortion of cristae and accumulation of material (thought to represent early calcification) on and between the cristae The myofibrillae were deranged and fragmented and were separated by accumulation of intracellular fluid The M bands contained many dilated sarcoplasmic reticula lipid droplets glycogen particles and sarcoplasmic ground substance Rupture of the sarcolemma and separation of myofibrils at intercalated discs were seen Finally nuclear changes occurred consisting of marginal clumping of chromatin loss of nucleoli and vesiculation Also edema of the vascular endothelium was noted

The sequence of structural abnormalities suggested that interference with magnesium dependent enzymes involved in oxidative phosphorylation played an important role in the pathogenesis of the lesions observed[11] The lesions were not similar to those produced by potassium deficiency or ischemia

✓ Several studies of magnesium deficiency have also been conducted in dogs Vitale and associates[12] reported calcification of the inner portions of the myocardium in magnesium deficient puppies Calcification of the aorta and medium sized arteries was also noted Wener and associates observed no gross changes in the hearts of young dogs (three to eight months old) studied after receiving a magnesium deficient diet for a mean of 87 2 days Light microscopic findings showed only degenerative vascular changes in the hearts of these dogs The endothelial cells of the intima showed pyknosis or absence of nuclei There also was a suggestion of edema of the media Segmental necrosis of some small coronary arteries was noted but changes in larger coronary arteries were not as striking Sections of myocardium revealed irregularly distributed small patches of hyperchromatic staining myocardial fibers frequently located adjacent to abnormal vessels Necrosis was seen in some areas of the myocardium and there were small areas of calcification in a few animals

Electrocardiograms recorded from magnesium deficient dogs revealed ST segment depression with flattening of the T waves in the precordial leads[3] The electrocardiographic changes were interpreted as nonspecific and not related strictly to serum magnesium levels The toxic effects of acetyl strophanthidin infusion (100 mg/min) were markedly increased in 19 mongrel dogs rendered hypomagnesemic by hemodialysis The arrhythmias resulting from digitalis toxicity were terminated by infusion of magnesium

✓ Moore and colleagues[13] observed focal cardiac necrosis and calcification in diet induced magnesium deficiency in calves Swelling of myofibrils and degeneration of Purkinje fibers were noted ✓

Magnesium deficient monkeys did not develop any histopathologic changes[15] However magnesium deficient monkeys were found to be more

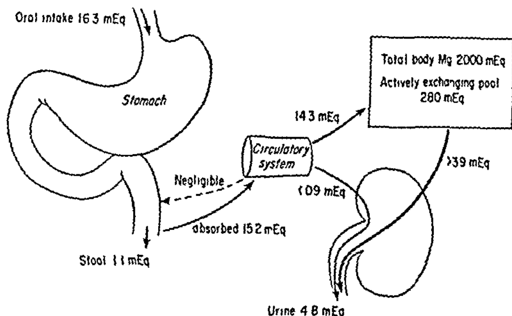


Fig 1 Diagram illustrating the daily turnover of magnesium in a normal woman The urinary excretion was determined through intravenous administration of Mg (From Yun T K Lazzara R Black W C, Walsh J J and Burch G F The turnover of magnesium in control subjects and in patients with idiopathic cardiomyopathy and congestive heart failure studied with magnesium 28 J Nucl Med 7 177 1966 Reproduced by permission)

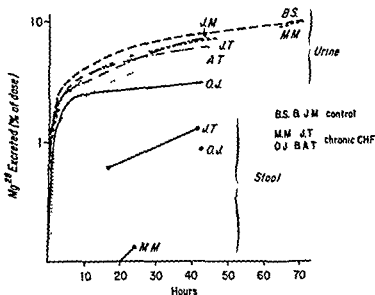


Fig 2 Time course curves of cumulative excretion of Mg for two control subjects and four patients with idiopathic cardiomyopathy and congestive heart failure who were given intravenous injections of the tracer element (From Yun T K Lazzara R Black W C Walsh J J and Burch G E The turnover of magnesium in control subjects and in patients with idiopathic cardiomyopathy and congestive heart failure studied with magnesium 28 J Nucl Med 7 177 1966 Reproduced by permission)

Magnesium in normal biochemistry and physiology

Magnesium activates many enzyme systems It is also a required co factor for oxidative phosphorylation[3,4] For example magnesium activates alkaline phosphatase and pyrophosphatases, and the magnesium ion is a necessary co factor when ever thiamine pyrophosphate is required Enolases and leucine aminopeptidase also require magnesium for their enzymatic activity These are extremely important enzymatic processes which are necessary for normal cell function and health In addition magnesium is involved in the structural integrity of ribosomal particles and protein synthesis

It is well known that a relationship exists between intracellular and extracellular sodium and potassium A similar relationship exists between calcium and magnesium In fact an interdependent relationship with magnesium exists for most if not all ions present in the body Moreover there is a relationship among all four major cations i e the intracellular ratios log (K)/(Na) and log (Mg)/(Ca) are related[4] There is evidence that membrane Na K dependent adenosine triphosphatase (ATPase) requires magnesium[4,7] Since this ATPase is necessary for the maintenance of a normal intracellular potassium magnesium is directly involved in the regulation of potassium

A decrease in either calcium or magnesium serum concentration results in increased neuronal excitability and neuromuscular transmission However the effect of calcium is opposite to that of magnesium in muscle Magnesium in large doses or concentration has a curariform action on the neuromuscular junction This action perhaps is produced by interference with the release of acetylcholine from motor nerve terminals[3,4]

the alcohol to the myocardium (2) nutritional disturbances (beri beri) (3) toxic effects of substances contained in alcoholic beverages (e g cobalt) and (4) a combination of the above [5]

Alcoholic cardiomyopathy is usually characterized predominantly by the symptoms and signs of left sided heart failure when the cardiomyopathy is advanced and the myocardial damage extensive [6] Initially alcoholic cardiomyopathy has mild to subtle manifestations often limited to the ECG It is becoming well established that alcohol alone is sufficiently toxic to produce myocardial damage The pathogenesis of alcohol induced cardiac injury may involve metabolites of ethanol (acetaldehyde) associated nutritional disturbances or electrolytic disturbances (hypomagnesemia itself) along with direct toxic injury to the myocardium

The cardiac changes produced by experimental *magnesium deficiency* in the rat *(vide supra)* are similar in many ways to the changes found in mice fed large quantities of alcohol [2,7] However histologic and electron microscopically observed structural changes are not specific Mitochondrial damage is *prominent in* both groups as well as disruption of myofibres and swelling and dilatation of sarcoplasmic reticulum Such ultrastructural changes have been observed in hearts of patients with alcoholic cardiomyopathy [2,29,30]

The electrocardiograms recorded from alcoholic patients reflect changes of magnesium deficiency Evans *described* the T wave changes associated with alcoholism to be of *four types* *(1)* bifid or cloven (2) spinous (3) isoelectric or (4) negative Flink and colleagues[3] reported ECG changes associated with magnesium deficiency resembling those of hypokalemia Only primary ST segment alterations were noted in acute alcoholism and these changes could be *corrected* only with magnesium therapy Because electrolyte imbalance for any one electrolyte is associated with changes in all electrolytes it becomes difficult to know which electrolyte is responsible for ECG changes

The early electrocardiographic manifestations of alcoholic myocardial disease are T wave and ST segment changes As the disease advances in severity and duration more extensive ECG changes reflecting diffuse myocardial damage occur These include widening of the QRS complexes conduction disturbances and arrhythmias such as atrial fibrillation There is a need to study in detail the ECG changes associated with magnesium depletion and repletion in alcoholic cardiomyopathy

Beri beri heart disease which may be found in alcoholics is characterized by a high cardiac output state predominantly right sided congestive heart failure (when congestive heart failure occurs) bounding pulses and peripheral neuropathy These changes have been attributed primarily to thiamine deficiency but alcohol intoxication and disturbances in magnesium metabolism may be important associated contributing factors Thiamine deficiency may also be associated with magnesium deficiency Because of the importance of magnesium in oxidative phosphorylation and as a cofactor for thiamine metabolism magnesium deficiency may worsen the symptoms and signs of thiamine deficiency *and unless* corrected may even prevent or considerably lessen the therapeutic effects of thiamine administration [3]

Electrocardiographic abnormalities and arrhythmias associated with *magnesium* deficiency

The *electrocardiographic* changes of magnesium deficiency (Fig 3) are *different from* those of potassium and calcium imbalance in experimental animals However *there is a* lack of agreement as to what ECG changes are characteristic of magnesium deficiency This is not surprising since it is unlikely that magnesium *deficiency* ever occurs entirely alone It has been shown that disturbances in balance of any one electrolyte result in changes of practically all the others [36] Magnesium does influence the *con*centration and distribution of the other major cations as well as important metabolic *pro*cesses

When children suffering from severe malnutrition are given nutrients without adequate magnesium supplementation the ECG reveals sharply peaked asymmetrical T *waves and* prominent U waves *similar* to patterns recorded by Vitale and associates for magnesium deficiency in dogs Prior to *replacement* therapy flat or inverted T waves *were* recorded in children Low voltage P waves and QRS complexes have been recorded in magnesium deficient patients These changes were reversed by magnesium administration Thus it would appear that early magnesium

Table I Causes of symptomatic hypomagnesemia*

I	*Gastrointestinal disorders*
	a Malabsorption syndromes including nontropical sprue
	b *Malabsorption due to extensive bowel resection*
	c Bowel and biliary fistulas
	d Prolonged nasogastric suction with administration of magnesium
	e Free parenteral fluids
	f *Prolonged diarrhea*
	g Protein calorie malnutrition
	h *Alcoholic cirrhosis*
	i Pancreatitis
II	*Endocrine disorders*
	a Hyperparathyroidism and hypoparathyroidism
	b Hyperaldosteronism
	c Diabetic coma
III	*Renal diseases*
	a Glomerulonephritis
	b Pyelonephritis
	c Hydronephrosis
	d Nephrosclerosis
	e Renal tubular acidosis
IV	*Alcoholism*
V	*Diuretic therapy (mercurials, ammonium chloride and thiazides)*
VI	*Malignant osteolytic disease*
VII	*Porphyria with inappropriate secretion of antidiuretic hormone*
VIII	*Excessive lactation*
IX	*Idiopathic*
X	*Cardiopulmonary bypass*
XI	*Soft water*

Modified from Wacker W E C and Parisi A F Magnesium metabolism N Engl J Med 278 712 1968 Reproduced by permission

susceptible to the toxic effects of digitalis than control animals It was proposed that this latter effect was due to intracellular loss of potassium produced by magnesium deficiency but this concept is certainly difficult to establish

Myocardial disease in magnesium deficiency in man

There are many causes of magnesium deficiency in man (Table I) It has been shown that magnesium deficiency in a healthy man is not very likely to be due to inadequate intake since an efficient mechanism is present for decreasing losses of magnesium in the urine and feces when intake is reduced[17]

Severe magnesium deficiency in man is manifested by hyperexcitability and occasional behavioral disturbances[18] Tetany convulsive seizures and other central nervous system disturbances have been described Manifestations of magnesium deficiency in man are much less clearly defined than those in experimental animals[1] Nevertheless, magnesium deficiency does occur in man and may contribute to disease states. Chronic, low grade magnesium deficiency may be much more common than is conventionally considered since magnesium is not studied regularly in clinical medicine as are sodium potassium and chloride

It is impossible in this presentation to consider all aspects of magnesium deficiency in man in relation to myocardial disease Therefore, the remarks to follow are limited to alcoholic cardiomyopathy electrocardiographic manifestations and disturbances in cardiac rhythm, and ischemic heart disease However, the physician may readily think of many other situations in which magnesium plays an important role in clinical medicine

Alcoholic cardiomyopathy Chronic ingestion of alcoholic beverages is associated with hypomagnesemia and decreased skeletal muscle potassium [9, 21] Since about 20 per cent of body magnesium is contained in skeletal muscles, a deficiency of magnesium in this tissue indicates a significant intracellular deficit throughout the body (including the heart) A linear relationship exists between retention of infused magnesium and the increment of increase in skeletal muscle magnesium [1] supporting the reliability of skeletal muscle magnesium as an index of total body magnesium status For obvious reasons the state of myocardial magnesium metabolism remains little known in alcoholics even though electrocardiographic data suggest that myocardial magnesium deficiency exists in alcoholics [3]

Alcohol may increase renal excretion of magnesium by a direct effect on tubular resorption or by increasing production of some metabolic intermediates that could bind magnesium ions as they are being excreted Other factors producing magnesium depletion in alcoholics include vomiting and diarrhea hyperhydrosis drugs and hyperaldosteronism in patients with cirrhosis of the liver and ascites [9] It is interesting that relatively high rates of urinary excretion of magnesium continue in alcoholics during alcohol withdrawal states despite low serum levels of magnesium [4]

The mechanisms for the production of heart disease in association with excessive ingestion of alcohol by man include (1) direct toxic injury by

sium protects against the development of dietary induced arteriosclerosis better than does calcium Also magnesium decreases blood lipids and blood coagulability The role of magnesium administration in ischemic heart disease if any probably relates to its cellular effects e g counteracting adverse effects of intracellular calcium protecting against loss of intracellular potassium and maintaining the integrity of subcellular structure

Possibility of magnesium deficiency as a conditioning factor for heart disease

Because magnesium is so important in the etabolic function and physicochemical state of ells a deficiency of magnesium could render a ell more vulnerable to insults from viruses oxins radiation and other noxious agents For xample in alcoholic cardiomyopathy magne ium deficiency may contribute to the develop nent of viral infection This concept of hypomag iesium or even hypermagnesium being condi ioning factors for viral infections of the heart and other cardiac diseases needs investigation

Cardiopulmonary bypass and magnesium deficiency

A decrease in serum magnesium has been reported following cardiopulmonary bypass during open heart surgery even though intracellular magnesium has been reported to increase slightly[5] Importantly conversion of cardiac arrhythmias following cardiopulmonary bypass may be assisted by magnesium therapy when hypomagnesemia is present

Use of magnesium in management of cardiac disease

The need in clinical medicine to measure serum concentration of magnesium in all patients with heart disease as is the practice for sodium potassium and calcium cannot be overemphasized Surely attention should be directed to possible magnesium deficiency in patients receiving any and especially oral diuretics [3] Depletion of magnesium occurs with the use of mercurial diuretics ammonium chloride and especially the thiazides with poor dietary intake[20] Other drugs known to cause hypomagnesemia are capreomycin viomycin and gentamicin [5] Large doses of gentamicin may also cause potassium loss[5, 3] possibly related to secondary aldosteronism It is

Table II Suggested guidelines for treatment of magnesium deficiency*

Day	Dose
	Intramuscular route (50% MgSO solution)†
1	2 0 grams (16 3 mEq) every 2 hours for three doses and then every 4 hours for four doses
2	1 0 gram (8 1 mEq) every 4 hours for six doses
3-5	1 0 gram every 6 hours
	Intravenous route (ampules of MgSO)
1	6 0 grams (49 mEq) in 1000 mL solution containing glucose plus any other electrolytes and other medications as indicated—infuse in 3 hours followed by 5 0 grams in each of 2 one liter solutions administered throughout the day
2	A total of 6 0 grams (49 mEq) divided equally in the total fluids of the day
3-5	The same as day 2

From Flink E B The py of m gnesium deficiency Ann N Y Acad Sci 162 901 1969 Reproduced by perm sion.
†This suppl es 3 grams or 260 mEq of magnesium

common clinical practice to order supplemental potassium therapy for patients receiving kaliuretic diuretics particularly when digitalis preparations are also administered Consideration should also be given to magnesium supplementation for such patients since hypomagnesemia also predisposes to digitalis intoxication The supplemental dosage of magnesium as well as of potassium should not be empirical but should be based on each patient s need In patients with congestive heart failure secondary to idiopathic cardiomyopathy a significant correlation exists between daily cumulative balances and renal clearances of magnesium and potassium[1] The kinetics of magnesium metabolism in normal people and in patients with congestive heart disease have been reported previously from our laboratory[2] Orally and intravenously administered Mg was excreted very slowly (less than 5 per cent in the first 24 hours and less than 2 per cent per day thereafter) in patients with congestive heart failure and idiopathic cardiomyopathy[2] The excretion of urinary magnesium in patients with congestive heart failure was primarily from the magnesium pool of the body with less than 18 per cent of the daily urinary excretion being derived from newly absorbed magnesium

Most patients with magnesium deficiency will have a reduction of 1 0 to 2 0 mEq /Kg of body weight Suggested replacement schedules re

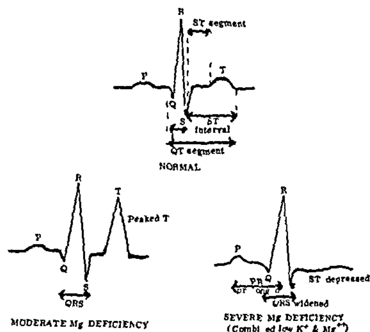


Fig 3 Electrocardiographic changes associated with magnesium deficiency (From Seelig M S Electrocardiographic patterns of magnesium depletion appearing in alcoholic heart disease Ann N Y Acad Sci 162 906 1969 Reproduced by permission)

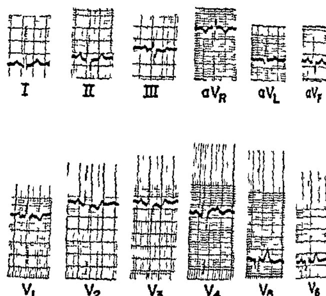


Fig 4 Electrocardiogram of a patient with alcoholic cardiomyopathy showing cloven and spinous T waves similar to those seen in magnesium deficiency (From Burch G E and Giles T D Diagnosis and treatment of cardiomyopathy in Changing concepts in cardiovascular disease the Proceedings of the American College of Cardiology Baltimore 1972 The Williams & Wilkins Company Reproduced by permission)

deficiency is characterized electrocardiographically by tall, peaked T waves (not narrow as in hyperkalemia) and a normal QT interval [44] These changes probably reflect in part a relative increase in extracellular potassium It is interesting that these T waves resemble the spinous T wave associated with alcoholism (Fig 4) [11, 44] Late or prolonged magnesium deficiency produces a prolonged PR interval, wide QRS complexes ST segment depression and low T waves [44]

Hypomagnesemia can contribute to disturbances in cardiac rhythm especially when associated with digitalis administration [7, 44, 4] Both digitalis administration and hypomagnesemia tend to produce a loss of intracellular potassium Hypokalemia produces electrical instability of the myocardium Significant intracellular deficit of these cations can be produced by oral diuretic therapy [43] It is not surprising therefore to find hypokalemia and hypomagnesemia in patients with heart disease since these patients frequently receive both digitalis (often in excessive amounts) and oral diuretics Administration of this combination of drugs contributes to the production of digitalis intoxication seen frequently in hospitals recently [44] Thus in the presence of hypomagnesium, as with hypokalemia, the amount of digitalis required to produce toxicity is reduced

It is prudent to obtain magnesium levels in the serum of any patient with digitalis induced arrhythmias of any type and to administer magnesium in treatment when levels are low [45] Such treatment has been shown to be effective in abolishing digitalis induced ventricular bigeminy and ventricular tachycardia Furthermore, when patients are hypokalemic intracellular potassium will remain low unless the associated hypomagnesium is also corrected

Cardiac arrhythmia has been reported in patients with hypomagnesemia even when the patients were not on digitalis therapy [46] In one patient, a paroxysmal supraventricular tachycardia was abolished by the intravenous administration of magnesium sulfate

Ischemic heart disease

The possible role of magnesium in the production of disturbances in the cardiac state of ischemic heart disease has been reviewed [4] Ischemic heart disease appears to be more prevalent in areas where people consume soft water than in areas where hard water (high calcium and magnesium) is consumed [47] Moreover the reported incidence of sudden death is greater in areas with soft water than in those with hard water

✓ It has been shown in the rabbit that magne

and Fraser R Magnesium deficiency after prolonged parenteral fluid administration and after chronic alcoholism complicated by delerium tremens J Lab Clin Med 43 169 1954
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gardless of the cause of the deficiency, are summarized in Table II As much as 2 mEq /Kg of magnesium chloride can be given over 4 hours and repeated 24 hours later However, replacement therapy should be determined by frequent evaluation of the patient with consideration of all aspects of the patient's health

There are not sufficient data to recommend the addition of magnesium to the drinking water of 'soft water' areas even though the incidence of ischemic heart disease and sudden death is greater in these areas than in areas with hard water containing higher concentrations of magnesium

General remarks

It is apparent that magnesium plays an important role in cardiac homeostasis and that magnesium deficiency is capable of producing cardiac disease Probably of more importance is the contributing role of magnesium deficiency to the pathogenesis of myocardial injury and the development of drug toxicity Magnesium deficiency will be found only when looked for and thus the responsibility for prevention detection and treatment resides with the physician The recognition of the importance of this ion leads to further realization that all elements contained within the body of man are important

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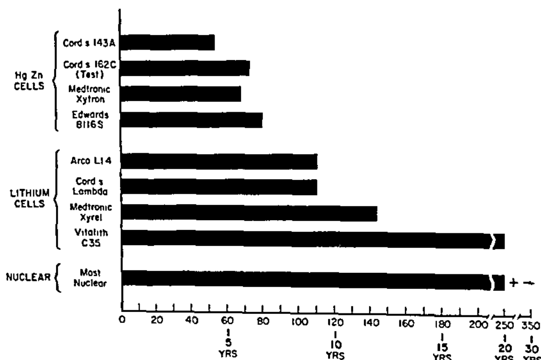


Fig 1 Projected longevity of power sources now in clinical use Calculations are based upon the known chemical content and energy density of the battery current required to operate the circuit and to produce a stimulating impulse and internal cell and circuit losses. (Data modified from information supplied by W Irnich)

imposed by venting of gas encapsulation and internal cell losses The newer power sources by their nature eliminate some of these problems and therefore offer a prolonged pulse generator life On paper at least pacemakers powered by lithium batteries are predicted to last 8 to 16 years and assuming that we will not be disap pointed once again nuclear batteries 10 to 30 years (Fig 1)

In selecting the proper pacemaker to use we are now confronted with an entirely *new set of* problems that require exploration including the impact of new local and Federal efforts to reduce medical costs

Relationship of pulse generator and patient longevity

A basic goal is to provide the patient with a pacemaker that will last the rest of his life without requiring replacement or further inva sive" intervention How will the present pace makers fulfill this objective?

Pacemakers are now implanted for many reasons other than complete heart block Obviously the expected longevity of patients with heart block differs from those with *sick sinus* syndrome or complex arrhythmias and no good data are available on the latter categories Our experience at the Newark Beth Israel Medical *Center* is comparable to that of others who responded to a national survey in 1975 indicating that in five years 44 per cent of patients had died About one quarter of the patients survived 10 to 15 years (Fig 2) Surprisingly many who survived that long were *not* originally in the youthful category and indeed some patients are still doing well in their late 80s It is evident that the selection of the correct pacemaker is not always easy

How often is battery failure the reason for pulse generator replacement?

The average age of pulse generators removed for battery exhaustion continues to increase (Fig 3) and pulse generator replacements represent a progressively smaller fraction of pacemaker oper ations (Fig 4) In the past two years it has gone from about 60 per cent to about 40 per cent

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Cardiac pacing and pacemakers VII
Power sources for implantable pacemakers
Part II

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Almost from the first the manufacturers of pacemakers predicted that there was sufficient energy stored in the battery to provide five years of pulse generator function It was a simple matter for them to measure the amount of current required to operate the electronic circuit, and to add the amount needed to stimulate the heart to arrive at a reasonable prediction Because many component, insulation, and wire problems caused frequent early failures it did not become obvious immediately that the five year prediction was extremely optimistic but soon enough it was clear that batteries were going to be a substantial problem In fact as late as 1970 a decade later many pulse generators still required replacement at 18 months

It was apparent for several reasons that the mercury/zinc cell of that era would rarely last more than 18 to 22 months In addition to the amount of current required to operate the circuit there were internal losses in the cell (self discharge) as well as energy consuming inefficiencies in the electronic circuit Moreover, cells decayed faster at body temperature than they did on the shelf

Table I lists some logical means of improving pulse generator life both then and now A multipronged attack on the problem was clearly indicated and happily has already been successful to a large extent (Table II) With these improvements the ideal pacemaker package is theoretically capable of lasting eight years (Even with older technology two such pulse generators were reported to have lasted 66 and 74 months[1,2])

Actually when only the energy density of available cells is considered and that in turn is translated into expected battery life mercury/zinc is, in fact a good power source Its longevity is compromised by the technical limitations

Table I

Defects	*Target for improvement*
Internal battery losses	More sophisticated battery design and construction
Limited battery capacity	Improved cell chemistry (new types of battery)
Short circuitry leaks (water metals) in package	Better insulation and encapsulation
High current drain in circuitry	New low drain circuits
High energy needed to produce cardiac response	Reduced current thresholds for cardiac stimulation

Table II

Target areas for improvement	*Recent accomplishments*
Battery design and construction	Double wrap Hg/Zn-Mallory RM 2
Cells	Lithium—many types Nuclear
Encapsulation	Hermetic sealing Isolation of battery from circuitry
Current drain	Hybrid and C Mos circuits (reduction from about 30 40 to 6 10 micro amps)
Threshold	Small electrodes and reduction in energy per impulse (reduced amplitude and pulse width)

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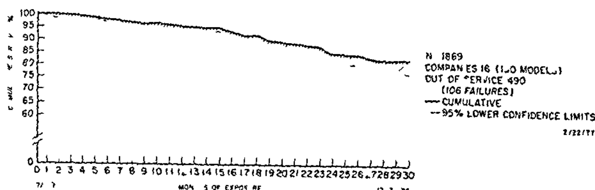


Fig 5 Cumulative survival of 1,869 pulse generators implanted since July 1 1974 at Newark Beth Israel Medical Center Montefiore Hospital, Bronx N Y and Los Angeles County/University of Southern California Medical Center At 30 months more than 80 per cent of the pacemakers are still functioning

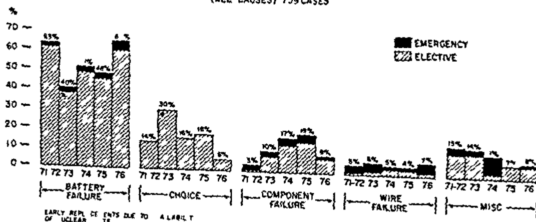


Fig 6 Major reasons for pulse generator replacement over a 6 year period at the Newark Beth Israel Medical Center Battery exhaustion is not the only reason for replacing a pulse generator

strenuous efforts to improve all links of the pacemaker system before we can realistically expect to have a lifetime pacemaker for everyone

At the same time that long life power sources were being developed the manufacturers recognized the need for perfect circuits that would last as long as the power source Hybrid and integrated circuits which can be encapsulated in hermetically sealed cans have in fact improved the reliability of some of the new pulse generators tremendously The track record of the lithium and nuclear pacemakers has been extraordinary There have been no known battery failures in 2300 nuclear implants and in thousands of lithium implants (Fig 8) Component failures have been so rare in these units that actuarial survival at three and four years is approximately 95 per cent

Part of this improvement has been brought about by the hermetic sealing of the batteries into the same package as the electronic components Hermetic sealing of mercury/zinc cells is not acceptable (although theoretically possible) because hydrogen gas is produced that must be vented through porous materials such as the epoxy resin capsule This is the reason that the electronic components in the Medtronic Xytron are encapsulated in a hermetically sealed can while the batteries are separately encased in

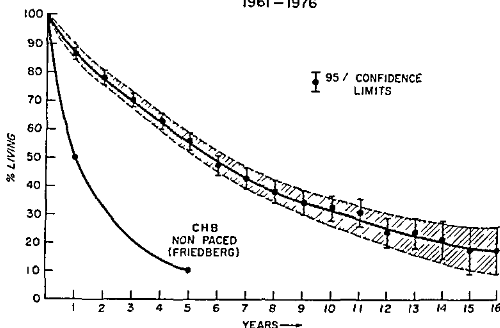


Fig 2 Survival curve of patients with implanted pacemakers treated at the Newark Beth Israel Medical Center

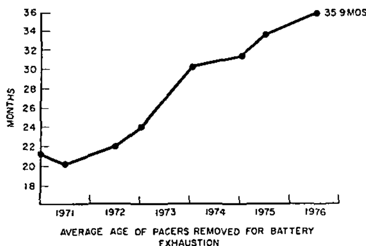


Fig 3 Figure illustrates the progressive increase in age of pulse generators removed for battery exhaustion

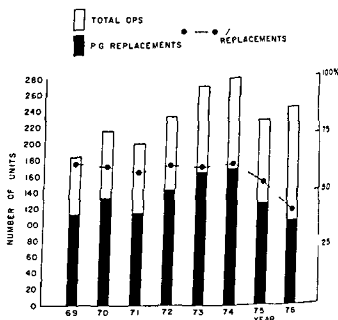


Fig 4 Number of pacemaker operations by year at the Newark Beth Israel Medical Center Pacemaker replacement is becoming less frequent

which reflects the improvement in the quality of our materials This is confirmed by the actuarial survival curves of new pulse generators (Fig 5) Furthermore, battery exhaustion now accounts for little more than half the pulse generator replacements (Fig 6) There remains a high incidence of wire fractures about 1 per cent or 2 per cent a year, that accounts for 5 to 8 per cent of reoperations, high thresholds add 5 to 8 per cent and the remainder are due to infection and extrusion of the pulse generator or wires and a variety of component failures [5] In those patients who survive three years about 30 per cent will require a reoperation on the pulse generator that has nothing whatever to do with the battery source (Fig 7) The long life batteries have therefore exposed some persistent old pacemaker problems as well as some entirely new ones that require new solutions Clearly there must be

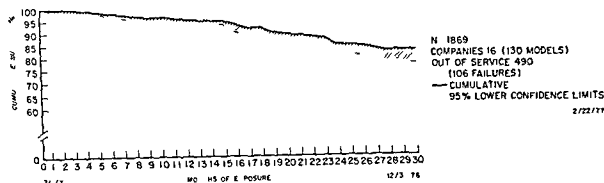


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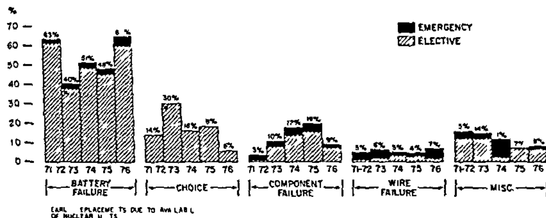


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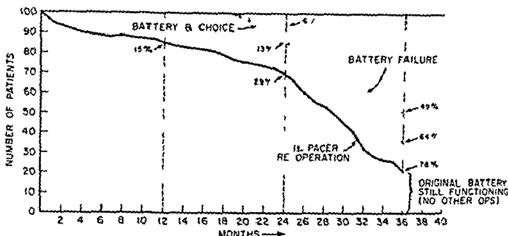


Fig 7 Reoperation required in 100 consecutive patients who lived for three years following pacemaker implantation at the Newark Beth Israel Medical Center At three years half the pulse generators had been replaced for battery but an additional 29 per cent required reoperation for other reasons

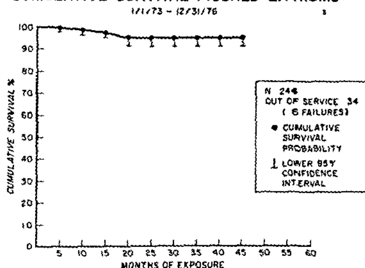


Fig 8 Cumulative survival of all lithium powered pulse generators (largely CPI) implanted at the Newark Beth Israel Medical Center since January 1973 At 45 months more than 95 per cent of implants are still in service

epoxy resin With appropriate getters (materials that absorb gases) it is conceivable that mercury/zinc cells also can be encapsulated in hermetically sealed cans but this is a more complex technique and is one of the reasons for deserting the mercury/zinc cell

Is a long life pacemaker enough?

If a pacemaker is to last a lifetime one must remember that sooner or later aging patients develop new medical problems that may require modification in pacemaker function For example although it is almost impossible to produce ventricular fibrillation by pacing the heart in the vulnerable period ventricular fibrillation thresholds may become lowered by disease states and drugs in rare instances it then may become possible to produce ventricular fibrillation accidentally Complex arrhythmias may occur that require new pacing modes, or no pacing at all All pulse generators and especially long life units should therefore be adjustable (programmable) Several models with rate and output adjustability are on the market and all manufacturers are hard at work developing such systems With the incredible versatility that is provided by the microcircuitry literally every function of the future pacemaker will be programmable rate output amplitude pulse duration refractory period, pacing mode and sensitivity A built in system to indicate the status of the battery and major components is also in the offing[7]

Are environmental hazards a problem?

This emotion packed question is hard to answer There are for example cogent arguments for and against nuclear units Nevertheless it is the current view that ^{238}Pu offers no significant risk to the adult patient and those around him disposal be it burial or cremation is not dangerous because plutonium dioxide cannot be volatilized even at crematory temperatures[8] Moreover at the present volume of use the material cannot be used by terrorists in any meaningful way

Lithium and mercury/zinc are dangerous in their own right Metallic lithium reacts violently when in contact with water and factory fires and explosions have been known to occur[9] To protect the workers from this danger extreme precautions are now taken by the manufacturer to control air humidity and other sources of aqueous contamination Mercury/zinc when cremated releases

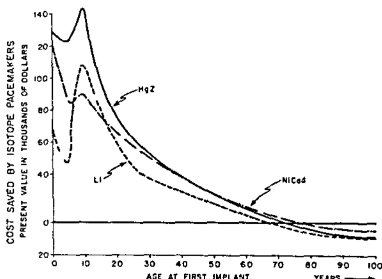


Fig 9 Comparative costs of nuclear lithium *(Li)* rechargeable *(NiCad)* and mercury/zinc *(HgZn)* pulse generators based upon calculations prepared by Coratomic These figures take into account the costs of the pulse generator and lead medical and hospital fees follow up visits inflation and interest rates, and expected patient and pulse generator longevity

mercury vapor an extremely toxic material into the environment [9] Thus no battery is without its environmental danger and there may be little to choose between one over the other in this regard

Will the cost of long life batteries be reasonable?

In the United States typical mercury/zinc pacemakers cost about $1 500 lithium units cost $2,200 and nuclear units cost $6 500 In 1975 new and replacement units were implanted at a rate of almost 10 000 a month At todays prices that represents an annual sale of approximately $?50 000 000 The prevalence of new pacemaker implants in the United States is 270 to 300 per million population the highest in the world and still rising rapidly These figures illustrate the impact of this growing technology on medical costs but they do *not* imply that we should use the simplest and cheapest pacemaker on every patient Obviously each individual deserves the best and most appropriate unit and it is up to the physician to decide what is best for whom

How to select the pacemaker for the patient

It is not difficult to select the proper pacemaker for an elderly patient whose associated medical illnesses clearly limit life expectancy But in light of expense what should one do for the otherwise healthy young or middle aged patient? When examining costs one must take into account the life expectancy of the unit the cost of follow up care and reoperation inflation rates etc Considering all these factors a nuclear pacemaker is probably the least expensive in the long run for all but patients over age 65 (Fig 9)

Nevertheless there has been a tendency to use lithium pacemakers rather than nuclear even in the young in the belief that one or two reoperations in a lifetime isn t so bad and that even if early replacement were required a new pulse generator might then be available that would last even longer

Still the ideal pulse generator should never require replacement and we should strive for this ideal This view is supported by our knowledge that infection of the operative site is more common after pacemaker replacement than at the primary insertion that surgery may be more complex with successive procedures and that each anesthesia represents a risk

There appears to be no tendency to continue with mercury/zinc pacemakers despite the fact that 6 to 8 year units would be sufficient for most patients and certainly a lot cheaper than

Table III New pulse generators implanted—1976

Mfg	HgZn	NiCad	Li	Nuclear	Total
Cordis	106	–	10	16	132 (54%)
CPI	–	–	52	–	52 (21%)
Medtronic	9	–	6	2	17 (7%)
Arco	–	–	8	1	9 (4%)
Medcor	2	–	5	–	7 (3%)
Intermedics	–	–	7	–	7 (3%)
Edwards	4	–	3	–	7 (3%)
Coratomic	–	–	4	2	6 (2%)
American Pacemaker	3	–	–	–	3 } (3%)
Pacesetter	–	2	–	–	2 }
Vitatron	2	–	–	–	2 }
Biotronic	1	–	–	–	1 }
Total	127 (52%)	2	95 (39%)	21 (9%)	245

anything else The swing to lithium has been almost revolutionary chiefly because lithium cells can be hermetically sealed and the total pulse generator package is quite small and more acceptable to the patient Our own records are indicative of such a change in attitude (Table III)

Based on present knowledge and technology, a reasonable plan for selection of the pacemaker is as follows

1 For a patient with clearly limited life expectancy select a pacemaker with a mercury/zinc or lithium battery preferably programmable

2 For a middle aged patient, select a lithium pacemaker, programmable unless the patient demands (and can pay for) a nuclear unit

3 For the young but fully grown adult select a nuclear pacemaker programmable

4 For a child select a small *non* nuclear unit, a longer life pulse generator can be substituted when reoperation is required to advance more wire into the heart

This brief analysis of available power sources for pacemakers has attempted to show the merits of some of the new batteries but has also tried to emphasize that advances in technology have extended the useful life of the older mercury/zinc cell as well Nevertheless the shift has been *away* from mercury/zinc, at least in the United States at an ever increasing pace, largely because the lithium and nuclear units may be totally encapsulated in a metal package and are smaller than anything available in the past This makes them more acceptable to the patient, decreases the chance of failure from fluid leaks and increases the potential longevity of the pulse generator Nuclear powered pacemakers will still be indicated in a small number of patients

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Veno occlusive disease of the liver

A characteristic form of hepatic injury termed veno-occlusive disease (V O D) is produced by pyrrolizidine alkaloids which are naturally-occurring potent hepatotoxins They cause necrosis of the endothelium of small hepatic veins resulting in their occlusion and blockage to the outflow of blood from the liver The early histologic changes in the liver include subendothelial edema of central veins with partial or complete occlusion centrilobular congestion and hemorrhagic necrosis of adjoining parenchymal cells With passage of time an essentially non portal type of fibrosis with a predominant centrilobular distribution is observed

The pyrrolizidine alkaloids are found in a large number of unrelated botanical families including Compositae (genus *Senecio*) Leguminosae (genus *Crotalaria*) and Boraginacae (g cera *Heliotropium* and *Trichodesma*) These plants have a world wide distribution and have mainly presented a veterinary problem causing extensive loss of livestock in Australia Africa and Central Asia

Human V O D of the liver was first recognized in Jamaica where it had been present in an endemic form and mainly affected children It was traced to be caused by the consumption of *Senecio* and *Crotalaria* plants in the form of bush tea. Small outbreaks and isolated instances have been reported from South Africa India as well as other countries and were caused by contamination of cereal with seeds of the toxic plants or their possible use in herbal medicine

The clinical features of hepatic V O D depend upon the amount and duration of exposure to the toxic alkaloids It may present acutely with epigastric pain and rapidly developing ascites as observed in many of the published reports The mortality in the acute stage may be considerable Complete recovery may occur as well as progression toward chronicity resembling cirrhosis of the liver

A large outbreak of hepatic V O D recently occurred in northwestern Afghanistan affecting several thousands of inhabitants. It was caused by contamination of wheat with seeds of *Heliotropium* plants The plants had multiplied profusely in the arid conditions during a period of drought which preceded the outbreak

The onset of the disease was insidious with abdominal discomfort and poor appetite After 3 to 4 months abdominal distension appeared and steadily increased, associated with wasting Extreme degree of ascites emaciation and edema of the lower extremities were present in late stages Fever jaundice and bleeding phenomena were rare The mortality was high, mainly due to remoteness and isolation of the villages and lack of adequate medical facilities The potential for recovery was, however revealed by the observation that six patients showed disappearance of all signs and symptoms following 3 to 9 months of supportive treatment in hospital Percutaneous liver biopsies were performed in three of them and did not show the characteristic lesions observed on initial examination

The Afghanistan outbreak appeared to be caused by consumption of minute amounts of toxic alkaloids over a period of several months. This conclusion was based on the observation that about 20 per cent of apparently normal inhabitants in the affected villages had evidence of disease indicated by hepatomegaly or hepatosplenomegaly Percutaneous liver biopsies in such early cases disclosed abnormalities typical of V O D

The chemical structure and metabolism of the pyrrolizidine alkaloids has been defined and their animal toxicity extensively examined These alkaloids are converted into highly reactive pyrroles probably by the liver cell microsomes which cause vascular damage In animals they induce lesions in lungs, kidneys, and other organs Hepatoma tumors of pancreas and urinary bladder have been produced in laboratory animals administered these alkaloids However in human toxicity significant lesions of organs other than liver have not been observed and there is no evidence of a carcinogenic effect

Appropriate action by public health, veterinary and agricultural authorities should prevent the occurrence of hepatic V O D in man and animals.

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Early ambulation following myocardial infarction

Several workers have already shown that early ambulation and discharge following acute uncomplicated myocardial infarction does not result in any increase in morbidity and mortality rate Recently in a prospective randomized controlled investigation in which ambulation after 5 days (with discharge after 12 days) was compared with ambulation and discharge on day 13 and day 19 respectively it was shown that the morbidity and mortality rate was significantly reduced during the year of follow up in the early ambulation group and particularly in patients who already had complications of their acute myocardial infarction on admission

It has also long been known that age has an adverse effect both on the short term and long term morbidity and mortality rate of patients with acute myocardial infarction Thus in patients with uncomplicated myocardial infarction who were kept at bed rest for 12 days after admission there was a 32 per cent complication rate during the first year in those under the age of 60 as opposed to 71 per cent in patients over the age of 60 years If patients who already had complications on admission were considered the corresponding figures were 69 per cent and 91 per cent respectively On the other hand if these patients were mobilized early (5 days) then the complication rate averaged 24 per cent regardless of the age of the patient or his state on admission

Thromboembolic complications seem to be particularly reduced Of nine patients who suffered from thromboembolic phenomenon eight were in the late ambulation group (pulmonary embolism four arterial embolism or thrombosis four) and only one patient had an arterial thromboembolic complication in the group who were mobilized early

It is obvious that no hard and fast rules can be laid down in the management of the individual patient with acute myocardial infarction and certainly it would be most illogical to mobilize him during the acute phase of any complication that may develop However the above studies indicate that age and the fact that complications had been present are no contraindication to early mobilization and our policy as in the studies reported has been to count the 5 days of bed rest from the first day that the patient's immediate symptoms or complications were satisfactorily treated and under control

Whether 5 days is the optimum period of bed rest is not known and indeed at least one study has shown no ill effects in patients with uncomplicated myocardial infarction who were mobilized 2 days after their admission

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Hypertension control, compliance and science

Recognition of the toll of disability and untimely death resulting from high blood pressure and realization that its treatment does more good than harm have brought students of hypertension out of their wet labs and sub specialty wards and into the marketplace the Goldblatt kidney risks replacement by the Gimbel hypertension control program

Although thoughtful evaluations of community programs for the detection and treatment of hypertension are few they underscore two lessons (1) Each of six requirements detection linkage to a clinician appropriate work up adequate treatment high medication compliance and lifelong follow up must be met before the patient benefits and a failure to

satisfy a latter requirement nullifies all prior efforts however effective (?) In abandoning the ivory tower for the shopping plaza, we must be careful not to abandon the scientific method for any collection of hopes homilies, and unconfirmed conventional wisdom when designing programs to achieve the community control of hypertension These strategies for hypertension control though they invoke disciplines foreign to the laboratory or clinical investigator are subject to the same rules of evidence and should no more be placed in general use without prior validation than should unproven drugs or untested surgery

Both of these points have been underscored again in a series of randomized trials recently carried out in collaboration with industrial and community physicians in our town

Screening of a random sample of employees at Dominion Foundries and Steel Limited yielded 245 men who had hypertension (when sitting quietly on three separate occasions, a standard series of fifth phase diastolic blood pressure readings were ≥ 95 mm Hg) were free of remediable forms of hypertension and were taking no daily medications Because teaching patients about their disease and its treatment is a time-honored approach to gaining their cooperation and because the convenience of follow up care had been suggested as an important determinant of compliance we tested these two strategies in our first randomized clinical trial.

These men were randomly assigned to receive or not receive instruction about hypertension its effects on target organs health and life-expectancy the benefits of therapy the need for high compliance and some simple reminders for pill taking Although subsequent tests showed that they mastered this information they were no more likely to take their medicine than men who received no instruction and we could demonstrate no correlation between knowledge and compliance For care and follow up these men had been randomly allocated to see either their own family doctors outside working hours or industrial physicians at the mill during work shifts the added convenience of follow up at work had no effect upon medication compliance either Thus two commonly proposed strategies for improving medication compliance in hypertension when subjected to the randomized experiment could not be shown to be useful.

Our second clinical trial was carried out to determine whether a more behaviorally-oriented set of strategies could salvage men who remained uncontrolled and non-compliant at the end of our first trial. Thirty eight such men were allocated either to a control group or to an experimental group who were taught how to measure their own blood pressure asked to keep records of their blood pressure and medication taking shown how to tailor the latter to the performance of daily habits and ritual, and seen fortnightly by a high school graduate with no formal health professional training who rewarded them for improvements in compliance and blood pressure control Six months later average compliance had fallen a further 1 5 per cent among controls but rose 21 3 per cent in the experimental group 30 per cent of whom achieved goal blood pressures This encouraging initial result if confirmed by other investigators, could mean that effective compliance-improving strategies might be applied maintained and supervised by a layperson without demanding either more time from a busy clinician or more reorganization from a beleaguered health service

However adherence to the scientific method calls for caution in interpreting even the results of randomized trials such as these For example although the results of our second trial were statistically significant they are based upon only 38 men. Furthermore our compliance improving strategies influenced the treating clinicians (who often increased the "vigor" of the treatment regimen) as well as the hypertensive patients, and quantifying the contribution of the former to the net result requires further research. Finally we do not yet know which of the individual components of the compound strategy tested in our second trial was responsible for the successful result fortunately a third trial addressing this issue is now being analyzed

Returning to the two lessons which began this invited annotation First only half of the hypertensive men we studied were taking enough medication at six months to show systematic declines in their diastolic blood pressures the other half were not realizing the benefits of blood pressure reduction and had nullified the previous effort and expense of their detection and evaluation. Second the application of the scientific method to the problem of compliance with antihypertensive medications permitted us to distinguish those commonly recommended strategies which may be clinically useful from those which are not

Surely we need further trials to confirm or refute the value of these and other strategies purported to satisfy each of the requirements for the control of hypertension

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Of bellyache

Babies and small children with "colds" or upper respiratory tract infections (URI) frequently cry with abdominal and epigastric pain. The URI without microbiologic isolations and detailed investigations are attributed to a viral agent, and the epigastric and abdominal pain to "intestinal colic." But the evidence to support the etiologic diagnosis or pathogenesis for the pain is usually lacking. The diagnosis of intestinal colic may be applicable in some instances. This is an old traditional concept based upon little study. However, from recent studies[1-3] *it seems likely that the abdominal pain could represent acute viral pancreatitis.* Many of the viruses that produce URI in man, especially in very young people, are small and are associated with a viremia. They can produce generalized arteritis (the possible beginning of arteriosclerosis), phlebitis, valvulitis, myocarditis, pericarditis, sympathetic ganglionitis, hepatitis and many other organ infections including pancreatitis (even with juvenile diabetes at times) and *bellyache* from viral pancreatitis and/or myenteric plexus neuritis. Do not ignore the bellyache; it may not necessarily be merely benign intestinal colic. It may be pancreatitis. Many serious illnesses, including viral heart disease, start with a URI and are heralded with a "bellyache."

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Small atrial septal defects

To The Editor

I was very interested by the article by Andersen and associates on "The natural history of small atrial septal defects Long term follow up with serial heart catheteriza tions. It contributes much to our incomplete knowledge of the long term hemodynamics in patients with this problem. I agree with their and others[2,3] appreciation of the potential inaccuracy of the pulmonary to-systemic flow ratio and their recommendation to consider the presence or absence of dia stolic flow murmurs ECG changes, heart enlargement and increased pulmonary vasular markings when deciding whether a patient has a large or small atrial septal defect There is one hemodynamic measurement that they did not include in their article which I would be very interested for them to examine in their 26 patients in which serial catheterizations were performed In this type of small atrial septal defect the mean left atrial pressure may be slightly higher usually 1 to 3 mm Hg, than the mean right atrial pressure if the cross sectional area of the defect is not over 2 square cm. This difference in mean atrial pressures if present suggests local (at the atrial septal level) resistance to flow I wonder whether the four patients in their series with significantly increased left to right shunts on recatheterization lacked this pressure differ ence initially If the pressures were equal, more frequent follow up or consideration of surgery might be indicated This small but significant pressure difference between the atria would appear to compliment the other prognostic factors they list and may be the most helpful It would further extend our knowledge of the natural history of small atrial septal defects if they would analyze this factor in their group of patients

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Reply

To the Editor

We wish to thank Dr Katholi for his comments on our article At his suggestion we looked through our material in order to see if there were any differences in mean pressures between right and left atria at the initial examination Unfortunately our material is not relevant in that respect at the initial examination the left atrium was not entered with the catheter in three of the four patients with later significantly increased left to-right shunts. In the remaining patient the catheter had to be withdrawn from the left atrium before the pressure was recorded because the patient experienced chest pain for some unknown reason

All told in 17 of our material of 26 patients either the left atrium was not entered or the recording was technically unsatisfactory Among the remaining nine patients there were no differences in mean pressures between the right and left atrium in three patients a difference of 1 mm Hg in two patients, and a difference of 2 mm Hg in four patients

We regret that we are not able to contribute to the point raised by Dr Katholi, a point which we think is well taken

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Truncus Arteriosus Communis

To the Editor

We have read the article "Truncus Arteriosus Communis Clinical angiocardiographic and pathologic findings in 100 patients" by Calder and associates which appeared in American Heart Journal in the July 1976 issue and also the Editorial by Jesse E Edwards in the same issue

We have analyzed 197 hearts of truncus pathologically of which we reported 180 in *The Journal of Thoracic and Cardiovascular Surgery* We believe that it is not wise to classify truncus, because of the numerous factors involved It is best to treat truncus in a factorial analysis in each individual case These factors are (1) the origin of the pulmonary tree—the factor so well worked out by Collett and Edwards (2) the place of origin of the truncus—that is from the right ventricle the left ventricle or both (3) the amount of pulmonary flow (4) the presence or absence of the hypoplastic aorta type of truncus (5) the presence or absence of truncus stenosis or insufficiency and ventricular septal defect stenosis and (6) atypical truncus Any one case may vary in the evaluation of each individual factor

The classification proposed by Calder and associates which divides truncus into (a) with ventricular septal defect and (b) without ventricular septal defect is in our opinion not wise For in our series 99 5 per cent of cases fall into the first category Only one member is found in the second category a case which we have published in the *American Journal of Cardiology* To our knowledge this is the only bona fide case of this sort in the modern literature Even though the classification by Calder and associates may be semantically

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Letters to the Editor

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We have analyzed 19? hearts of truncus pathologically of which we reported 180 in *The Journal of Thoracic and Cardiovascular Surgery* We believe that it is not wise to classify truncus because of the numerous factors involved It is best to treat truncus in a factorial analysis in each individual case These factors are (1) the origin of the pulmonary tree—the factor so well worked out by Collett and Edwards (2) the place of origin of the truncus—that is from the right ventricle the left ventricle or both (3) the amount of pulmonary flow (4) the presence or absence of the hypoplastic aorta type of *truncus* (5) the presence or absence of truncus stenosis or insufficiency and ventricular septal defect stenosis and (6) atypical truncus Any one case may vary in the evaluation of each individual factor

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pure our conception of a *practical classification is one in which a sizable number of members are found in a category*

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Reply

To the Editor

I would like to thank Dr Bharati for publicly expressing her opinions concerning the classification of truncus arteriosus communis

She says it is not wise to classify truncus because of the numerous factors involved This is precisely why we think a good classification is helpful—*because* numerous factors are involved If numerous factors were not involved then no classification would be needed If truncus were only one malformation then no classification would be required However there are in fact several very different anatomic types of truncus A good classification is helpful in grouping the different anatomic types for the purposes of many different types of study clinical hemodynamic angiocardiographic surgical pathologic and embryologic If the different anatomic types are not identified and separated then the results of the study must show wide variation leading to confusion In the investigation by Calder and associates the data were separated into anatomic types This made it possible for distinctive features of the various anatomic types to emerge as the interested reader will see This is regarded as important in order to facilitate more precise anatomic diagnosis which in turn is basic to successful surgical correction

Dr Bharati refers to the classification of truncus that was proposed by Calder and associates in July 1976 The classification used by Calder and associates was in fact proposed more than a decade ago by Van Praagh and Van Praagh (Am J Cardiol 16 406 1965) Our classification was proposed in order to correct the deficiencies of Collett and Edwards classification (1) Their type IV was a mistake Edwards has recently graciously conceded this (his Editorial July 1976) (2) Absence of a pulmonary artery branch is a hemodynamically and surgically important variable (3) So is interruption atresia or coarctation of the aortic arch (4) The ventricular septum rarely can be intact which also can be important and should be generally known

Dr Bharati states that our division of truncus into cases with a ventricular septal defect (VSD) (type A) and cases without a VSD (type B) is not wise Although rare truncus with an intact ventricular septum definitely *does* occur (Br Heart J **5** 97 1943 Am J Cardiol **16** 406 1965 Circulation **40** III 199 1969 and unpublished observations)

In my judgment Dr Bharati s bottom line is wrong She states that a *practical* classification is one in which a sizable number of members are found in a category The function of classification is to represent all important types frequent and infrequent Today when truncus is a surgically correctable malformation it certainly is not practical to ignore infrequent types

In the definition and classification of congenital heart disease what is wise? I would say Stick to the anatomic facts *all* of them Don t ignore any of them because basically you can t The anatomic facts keep on recurring Adherence to all of the anatomic data is a general principle of great importance in the taxonomy of congenital heart disease

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TAC and aorticopulmonary septal defect

To the Editor

There are a number of reasons for disagreeing with Dr Van Praagh s view of truncus arteriosus communis (TAC) Aorticopulmonary septal defect (APS) is not TAC

Calder and associates have described TAC as resulting from atresia of the subpulmonary infundibulum with partial or complete absence of the pulmonary valve and an aorticopulmonary septal defect In an evaluation of eleven specimens of hearts with A P S only one showed hypoplasia of the subpulmonary infundibulum In the other ten specimens the subpulmonary infundibulum was wide and the pulmonary as well as the aortic valves were normally formed How then can the presence of subpulmonary infundibulum and the presence of a pulmonary valve in APS be consistent with a diagnosis of TAC which is defined as having atresia of the subpulmonary infundibulum?

Secondly it is quite simple in diagrams to show that the aortic and pulmonary valves are together in APS (Fig 1) However on closer examination of the specimens tissue comprising walls of the aorta and the pulmonary trunk is always present between the two valves (in my limited experience) (Fig 2 *arrow*) What is the significance of this septum? To me it indicates that a division of the TAC into the two great vessels has taken place Following such a division it would be as unjustified to define APS as TAC as single atrium in the presence of a small but *definite atrial septum* Dr Van Praagh s analogy regarding single atrium common ventricle and TAC can be looked at in reverse The atrium develops as a single chamber—the single atrium When a septum has formed it is no more a single atrium The deficiency in the septum is referred to as atrial septal defect Similarly when a ventricular septum has formed it is not called common ventricle The

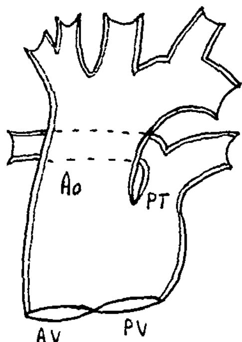


Fig 1 Aorticopulmonary septal defect The aortic valve (*A V*) and the pulmonary valve (*PV*) are together as usually shown diagrams.

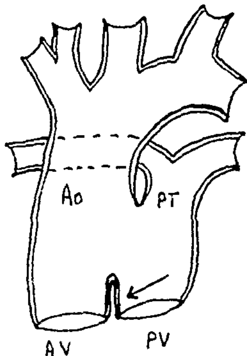


Fig 2 Aorticopulmonary septal defect The aortic valve (*A V*) and the pulmonary valve (*PV*) are separated by a septum (*arrow*) The septum represents the walls of the aorta (*Ao*) and the pulmonary trunk (*PT*)

ficiency is called a ventricular septal defect Lastly the ntral aorta with the sixth arch is the truncus arteriosus mmunis. When a septum has formed and the single truncal ive has divided into the aortic and pulmonary valves it is no ore TAC but an aorticopulmonary septal defect

Dr Van Praa h has concluded that the typical TAC is seudotruncus (tetralogy of Fallot with pulmonary infundib lar atresia) with partial or complete absence of the pulmo ary valve and with partial or complete absence of the orticopulmonary septum In association with Dr Edwards I ave had the opportunity of describing the specimen of a heart s tetralogy of Fallot with APS I wonder what name Dr Van raagh would like to give it Also if TAC is so closely related o extreme tetralogy (with pulmonary atresia) how is it that ot a sin le case of extreme tetralogy is on record with an ortic valve showing four cusps seen in almost a third of the ases of TAC described by Calder and associates This also ndicates that the valve of the TAC is not the aortic valve but the true truncal valve A quadricuspid aortic valve is not known in tetralogy or in APS and does not occur with such frequency in any other congenital cardiac lesion

Finally the surgical implications of TAC with one valve and A P.S wi h two valves are entirely different There is practical justification in separating the two conditions

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Reply

To the Editor

I would like to thank Dr Tandon for his letter concerning truncus arteriosus communis (TAC) and aorticopulmonary (AP) septal defect

Basically Dr Tandon disagrees with our view of TAC because he assumes that the classical embryological interpre tation of TAC is correct whereas we do not Instead our definition of TAC is based on the pathologic anatomy not on embryologic interpretation Moreover we think it is useful from the practical standpoint to distinguish between AP septal defect and AP septal absence because they are different surgical problems

The classical embryological interpretation of TAC is that the truncal cushions fail to grow downward from the junction of aortic arches four and pulmonary arches six Consequently the truncal valve is not divided into aortic and pulmonary valves and the ventricular outflow tracts beneath the undi vided truncal valve are not septated Thus g nuine cases of

TAC should have only one semilunar valve according to the classical theory preferably with four leaflets and there also should be a ventricular septal defect (VSD)

Since Dr Tandon still believes the classical interpretation of TAC he objects to our saying that it is possible to have TAC with two semilunar valves and an intact ventricular septum—our TAC type B (In our classification TAC with a VSD is type A[1]) Based on the conventional interpretation Dr Tandon thinks that our cases of TAC type B really are examples of AP septal defect and should therefore be excluded from the category of TAC

If I had not studied the problem I might very well have agreed with Dr Tandon I understand his view perfectly The basic problem with Dr Tandon s position is that the classical embryological interpretation on which it is based is not supported by the anatomic findings Briefly we think that the classical interpretation is partly wrong Unfortunately the conventional view of the truncal valve appears to be erroneous

Detailed study of the pathologic anatomy of the truncal valve in 57 autopsied cases led us to the following conclusions

1 When the truncal valve is tricuspid as it was in about two thirds of our cases of TAC the truncal valve was anatomically indistinguishable from the aortic valve

2 When the truncal valve is quadricuspid as it was in about one third of our cases the truncal valve appeared to be composed of three aortic leaflets plus a fourth leaflet—often longer (from commissure to commissure) and taller (from free margin to truncal mural attachment) than the other three leaflets This fourth leaflet we interpreted as a pulmonary leaflet remnant

Never did we find in fact what we expected to find based on the conventional embryologic theory Never did we find a common semilunar valve (analogous to a common atrioventricular valve) composed of aortic leaflet and pulmonary leaflet components in common—undivided Instead we found that the pulmonary leaflets were usually absent (when the truncal valve was tricuspid) or rudimentary and malformed (when the truncal valve was quadricuspid)

We realized that one could not base a defining criterion (that TAC have one semilunar valve only) on an erroneous concept (that TAC typically has a common or undivided semilunar valve)

How then should TAC be defined? Anatomically of course Not in terms of embryologic theory but in terms of anatomic fact In 1965 we wrote[1] The criteria of Lev and Saphir were employed for the anatomic diagnosis of truncus arteriosus (1) only one great artery arises from the base of the heart and (2) this great artery gives rise to the coronary arteries to the pulmonary arteries and to the systemic arteries

Dr Tandon states at the end of his second paragraph that we define TAC as having atresia of the subpulmonary infundibulum This is not correct Dr Tandon is confusing our embryologic interpretation with our definition

We think it is an important general principle that the definition and diagnosis of the various types of congenital heart disease be based on the pathologic anatomy rather than on embryologic theory because the pathologic anatomy is relatively constant whereas embryologic theory is prone to change

We think that all of us should regard our various embryologic hypotheses with the caution that they so richly deserve. The present lack of definite knowledge concerning the embryology of TAC merits emphasis More work is clearly needed in this area

If one is prepared to accept the aforementioned classical anatomic definition of TAC[3] embryologic preconceptions notwithstanding then TAC type B certainly exists. For example we published a case in 1965 (our Fig 4) and Bain and Parkinson[6] published a case in 1943 Moreover absence of the AP septum was Collett and Edwards[7] TAC type 5B Dr Jesse Edwards recently reiterated that he still regards absence of the AP septum as a partial persistent truncus. I would agree that absence of the AP septum must not be excluded from the category of TAC as Dr Tandon suggests, because the ascending aorta and the main pulmonary artery are anatomically in common—undivided

But Dr Tandon is most understandably worried that TAC with two semilunar valves and an intact ventricular septum (type B) is basically a different disease from the much more frequent TAC with a VSD (type A) I shared the same worry However I am certain that TAC type B and TAC type A are developmentally closely interrelated and this conclusion is strongly supported by two additional cases of TAC type B that we plan to publish in detail The salient findings are as follows

1 There is no remnant of the AP septum between the semilunar valves or above them The ascending aorta and the main pulmonary artery are totally in common—undivided.

2 The conal septum (that contributes to the parietal band) is very abnormally formed In one (Dr André Davignon s case from l Hopital Ste Justine in Montreal Canada) the conal septum (parietal band) is mainly fibrous very incompletely muscularized and transilluminates brilliantly In the other (Dr Lucy Swift s case from St Luke s Hospital Columbia Presbyterian Medical Center in New York City) the conal septum (parietal band) is present but very hypoplastic

3 The septal band is normally formed in both as is usual in TAC

4 The ventricular septum is intact in both

5 The semilunar valves are separate but abnormally formed in both In Dr Davignon s case the leaflets of both semilunar valves are somewhat thickened as one often sees in TAC In Dr Swift s case aortic valvular atresia and a blind left ventricle are present

These cases are *more* than a large AP septal defect Particularly in Dr Davignon s case the mainly fibrous conal septum (central portion of the parietal band) is very impressive The conal septum almost didn t make it This case of TAC type B almost was a TAC type A—a VSD was very nearly present

Hence I am sure that TAC type B is indeed a form of TAC and that it is closely related to TAC type A

But this should come as no surprise Almost everything in biology may be regarded as a spectrum Almost every anomaly has an incomplete form or forme fruste and TAC is no exception

One may regard absence of the AP septum as a partial form of TAC as Dr Jesse Edwards does Or as we stated in 1965 TAC type B may be regarded as the only isolated or 'pure form of common aorticopulmonary trunk i e without complete absence of the distal pulmonary infundibulum and without complete or partial absence of the pulmonary valve

Either way absence of the AP septum should not be excluded from the category of TAC

TAC type B is fascinating from the developmental standpoint The conventional embryologic explanation seems not to apply in the sense that there appears to have been virtually no downgrowth of the aorticopulmonary and truncal ridges The semilunar cushions and the conal cushions have septated their respective regions without the assistance of the more distal truncal and aorticopulmonary cushion tissue

Also the conal cushions appear to form the central portion of the parietal band The entire septal band appears to be a right ventricular structure not a conal structure

I agree with Dr Tandon that typical relatively small AP septal defect should of course be so diagnosed as in the cases mentioned in his second and fourth paragraphs

Concerning Dr Tandon s fourth paragraph, we would not expect the aortic valve in tetralogy of Fallot with pulmonary outflow tract atresia to be quadricuspid In TAC with a quadricuspid valve as mentioned above the fourth leaflet appears to be a pulmonary leaflet remnant We would not expect a pulmonary leaflet remnant in the aortic valve of patients with tetralogy The pulmonary leaflet remnants in extreme tetralogy appear to be sequestered away from the aortic valve on the pulmonary side by the intact AP septum.

We think that there are practical surgical reasons for distinguishing between septal defects and septal absences Just as a defect in the atrial septum (atrial septal defect) should be distinguished from absence of the atrial septum (common atrium) and just as a defect in the ventricular septum (VSD) should be distinguished from absence of the ventricular septum (a type of common ventricle) so too a defect in the AP septum (AP septal defect) should be distinguished from absence of the AP septum which is a type of common great arteries (TAC)

AP septal defect and AP septal absence are different surgical problems AP septal defect can be patched via a transaortic approach whereas absence of the AP septum requires surgical construction of a prosthetic AP septum

In summary there are sound anatomic embryologic and surgical reasons for not excluding absence of the AP septum from the category of TAC

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Now the treadmill!

To the Editor

Burch asks is man better off with the treadmill or not?" My objective evaluation (as a pathologist for the Medical Examiner) is a strong affirmative! Some 90 per cent of witnessed sudden and unexpected deaths are due to atherosclerosis In many cases these victims of silent heart disease" have had recent medical examinations including resting ECGs Clearly this is a Public Health problem!

The treadmill test a prognostic tool identifies those individuals who are at risk and the same treadmill results can be used therapeutically to write a safe exercise prescription

I have never seen fatal atherosclerosis in a non smoker with a normal Maximum Treadmill Stress Test Clearly this is a valuable test!

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REFERENCE

1 Burch G E Now the treadmill! (Annotation) Am Heart J 92 671 1976

Right aortic arch associated with contralateral congenital subclavian steal a well defined but certainly more frequent syndrome than reported on

To the Editor

In a paper by Pieroni and associates entitled Congenital subclavian steal Report of a case occurring in a neonate and review of the literature which appeared in the American Heart Journal (84 801 1972) the authors have made a review of the cases of congenital subclavian steal, the first case

TAC should have only one semilunar valve according to the classical theory, preferably with four leaflets and there also should be a ventricular septal defect (VSD)

Since Dr Tandon still believes the classical interpretation of TAC he objects to our saying that it is possible to have TAC with two semilunar valves and an intact ventricular septum—our TAC type B (In our classification TAC with a VSD is type A) Based on the conventional interpretation Dr Tandon thinks that our cases of TAC type B really are examples of AP septal defect and should therefore be excluded from the category of TAC

If I had not studied the problem I might very well have agreed with Dr Tandon I understand his view perfectly The basic problem with Dr Tandon s position is that the classical embryological interpretation on which it is based is not supported by the anatomic findings Briefly we think that the classical interpretation is partly wrong Unfortunately the conventional view of the truncal valve appears to be erroneous

Detailed study of the pathologic anatomy of the truncal valve in 57 autopsied cases[1] led us to the following conclusions

1 When the truncal valve is tricuspid as it was in about two thirds of our cases of TAC the truncal valve was anatomically indistinguishable from the aortic valve

2 When the truncal valve is quadricuspid as it was in about one third of our cases the truncal valve appeared to be composed of three aortic leaflets plus a fourth leaflet—often longer (from commissure to commissure) and taller (from free margin to truncal mural attachment) than the other three leaflets This fourth leaflet we interpreted as a pulmonary leaflet remnant

Never did we find in fact what we expected to find based on the conventional embryologic theory Never did we find a common semilunar valve (analogous to a common atrioventricular valve) composed of aortic leaflet and pulmonary leaflet components in common—undivided Instead we found that the pulmonary leaflets were usually absent (when the truncal valve was tricuspid) or rudimentary and malformed (when the truncal valve was *quadricuspid*)

We realized that one could not base a defining criterion (that TAC have one semilunar valve only) on an erroneous concept (that TAC typically has a common or undivided semilunar valve)

How then should TAC be defined? Anatomically of course Not in terms of embryologic theory but in terms of anatomic fact In 1965 we wrote The criteria of Lev and Saphir were employed for the anatomic diagnosis of truncus arteriosus (1) only one great artery arises from the base of the heart and (2) this great artery gives rise to the coronary arteries to the pulmonary arteries and to the systemic arteries

Dr Tandon states at the end of his second paragraph that we define TAC as having atresia of the subpulmonary infundibulum This is not correct Dr Tandon is confusing our embryologic interpretation with our definition

We think it is an important general principle that the definition and diagnosis of the various types of congenital heart disease be based on the pathologic anatomy rather than *on embryologic* theory because the pathologic anatomy is relatively constant whereas embryologic theory is prone to change

We think that all of us should regard our various embryologic hypotheses with the caution that they so richly deserve The present lack of definite knowledge concerning the embryology of TAC merits emphasis More work is clearly needed in this area

If one is prepared to accept the aforementioned classical anatomic definition of TAC[3] embryologic preconceptions notwithstanding then TAC type B certainly exists For example we published a case in 1965 (our Fig. [illegible]) and B[illegible] and Parkinson[4] published a case in 1943 Moreover absence of the AP septum was Collett and Edwards'[?] TAC type 5B Dr Jesse Edwards recently reiterated that he still regards absence of the AP septum as a "partial persistent truncus" I would agree that absence of the AP septum must not be excluded from the category of TAC as Dr Tandon suggests because the ascending aorta and the main pulmonary artery are anatomically in common—undivided

But Dr Tandon is most understandably worried that TAC with two semilunar valves and an intact ventricular septum (type B) is basically a different disease from the much more frequent TAC with a VSD (type A) I shared the same worry However I am certain that TAC type B and TAC type A are developmentally closely interrelated and this conclusion is strongly supported by two additional cases of TAC type B that we plan to publish in detail The salient findings are as follows

1 There is no remnant of the AP septum between the semilunar valves or above them The ascending aorta and the main pulmonary artery are totally in common—undivided

2 The conal septum (that contributes to the parietal band) is very abnormally formed In one (Dr André Davignon s case from l Hopital Ste Justine in Montreal Canada) the conal septum (parietal band) is mainly fibrous very incompletely muscularized and transilluminates brilliantly In the other (Dr Lucy Swift s case from St Luke s Hospital Columbia Presbyterian Medical Center in New York City) the conal septum (parietal band) is present but very hypoplastic

3 The septal band is normally formed in both as is usual in TAC

4 The ventricular septum is intact in both

5 The semilunar valves are separate but abnormally formed in both In Dr Davignon s case the leaflets of both semilunar valves are somewhat thickened as one often sees in TAC In Dr Swift s case aortic valvular atresia and a blind left ventricle are present

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CRC Handbook of Engineering in Medicine and Biology vol 1 By David C Fleming and Barry N Feinberg Cleveland 1976 CRC Press Inc 471 pages Price $44 95

This is an excellent handbook on biomedical engineering The recent interest of engineers and biophysicists in medicine and biology has stimulated biomedical research extensively This has been of considerable value even to clinical medicine where it is expressed primarily in the introduction and improvement of diagnostic and therapeutic devices. The average doctor will find it impossible to understand most of this book but it should interest those in research in medicine especially cardiology The 13 presentations include electrophysiology hemodynamic phenomena and computer systems, which are of especial interest to cardiologists The presentations are very good and practical Engineers as well as biologists and cardiologists should find this a profitable addition to their literatures

Intraaortale Ballongegenpulsation By Ernst Rainer de Vivie Berlin/Heidelberg/New York 1976 Springer Verlag

This brief paperback publication in German describes the principles of anesthesiology and resuscitation The figures and illustrations are numerous and the description of methods and results are standard but different in that there is considerate emphasis on physiologic principles For those who can read German this is a useful book.

Cardiac Emergencies Edited by Robert S Eliot Gerald L Wolf and Alan D Forker Mount Kisco New York 1977 Futura Publishing Company 375 pages Price $27 50

This third volume on *Contemporary Problems in Cardiology* edited by Eliot et al is not only timely but reviews problems of current emphasis in medicine and cardiology The book consists of a series of short papers related to pathophysiology diagnosis and management This is not a comprehensive presentation of the various selected subjects but rather a brief summary of the contributors concepts and practices Readers will find the presentations interesting even though some complex subjects are reviewed superficially such as the pathophysiology of congestive heart failure and cardiogenic shock in patients with myocardial infarction The contributors have effectively centered their considerations for the benefit of clinical practice Readers will have an opportunity to learn a great deal from this book. It is brief clearly written and nicely illustrated The material presented is fairly extensive and well done in less than 3 5 pages House staff and students will find the book a good source of information

Cardiac Arrhythmias Diagnosis and Treatment Second Edition Edited by Noble O Fowler Hagerstown Md 1977 Harper & Row Inc 236 pages

This second edition includes the new advancements in the management of cardiac arrhythmias including discussions of surgical section of the bundle of Kent and His bundle recordings The text of the book is 210 pages The book is concerned with the common arrhythmias, their pathophysiology and management The 12 contributors briefly review the problems of arrhythmias for the clinician The physician will therefore find this book to be practical and useful. The discussions present the management in detail so that the reader has no difficulty in applying the recommendations to his patient including electric conversion of arrhythmias The first edition has been well received and the second edition should continue this reception This is a good practical book.

Myocardial Infarction Edited by E. I Chazov Chicago 1976 Imported Publications Inc (Mir Publishers Moscow) 380 pages. Price $6 80

Chazov is one of the outstanding cardiologists in USSR He has edited a book which describes for cardiologists of other nations the approach to myocardial infarction in Russia The translation from the Russian to English was by David A Myshne The book consists of nine chapters dealing with pathology pathogenics epidemiology clinical manifestations complications, diagnosis and management It is a good publication which indicates that the Russian approach to myocardial infarction is the same as that in the western world. This is an interesting and good book which should be read by those who wonder what the practice of cardiology in Russia is like

Basic Correlative Echocardiography—Technique and Interpretation By Siegfried J Kra M D Flushing New York 1977 Medical Examination Publishing Company Inc 270 pages. Price $14 00.

This manual on echocardiography represents a training source for beginners in the field The tracings are very good They were selected from many sources. ECHO is concerned primarily with adequate recordings and their interpretations References to patterns in the text could be supported better by more illustrations to assist the reader to understand properly actual ECHO manifestations. However this small book is useful and a good addition to those already available on ECHO Students housestaff and fellows in training in cardiology and internal medicine will find this to be a good book to own and study

Textbook of Echocardiography By Vincent E Friedewald, Jr M D Philadelphia 1977 W B Saunders Company 317 pages. Price $17 50

Books on echocardiography have been appearing at a rapid rate This is to be expected in view of this rapidly expanding field and instrumentation There is a need however for more trained technicians and echocardiographers This book by Friedewald is a good one The subject is presented in a well organized and thorough manner It is intended for trainees and includes a discussion of the physics of sound methodology principles of interpretation and a discussion of recordings of different structures of the normal and diseased heart This is a reliable and well organized book with a good appendix of normal values for reference

of which was reported on by Massumi in 1963 These authors have shown that the number of these cases was rapidly increasing indicating that the occurrence was more frequent than previously thought We are in agreement with this opinion

Becker and associates[3] have presented a comprehensive review of the congenital anatomic potentials for subclavian steal Fifty five potential causes have been described With this classification it is possible to foresee all cases of congenital subclavian steal Among these possibilities an entity can be individualized the association of a right aortic arch with contralateral congenital subclavian steal of which Pieroni and associates have found 17 cases angiographically documented in the literature in 1972

Embryologically this association can be understood by the diagram of Edwards who has employed a hypothetical double arch system the interruption of which at different locations explains the three main subtypes classified by Stewart and associates[5] and by Victorica and associates (1) right aortic arch with isolation of the left subclavian artery (as one of our cases seen in a 33 year old woman associated with ventricular septal defect but without cardiac or neurologic symptoms) (2) right aortic arch with aberrant and atretic left subclavian artery (as a case of Pieroni and associates[1]) (3) right aortic arch with mirror image branching of the arch vessels and atresia of left common carotid and left subclavian arteries (as the case of Levine and associates)

Clinically the diagnosis is suspected by the difference between the blood pressure and the radial and antecubital pulses of the right arm which are normal and of the left arm which are markedly diminished or absent Chest roentgenograms with barium swallow are useful to reveal esophageal indentations made by the right aortic arch and an aortic diverticulum (as in the subtype 2 of the classification of Victorica and associates[6]) The proof of the subclavian steal is given by aortography Injection of contrast material into the ascending aorta shows a right aortic arch with filling of the left common carotid or the left innominate artery right common carotid and right subclavian artery in that order The left subclavian artery does not opacify from the aorta Serial studies at 2 to 3 seconds after injection reveal opacification of the left subclavian artery which fills by retrograde flow down the left vertebral artery

There were usually no symptoms of vertebro basilar insufficiency during childhood Cerebral symptoms can appear in the third decade and the congenital subclavian steal needs then to be corrected by a graft placed between the ascending aorta and the left subclavian artery–left vertebral artery junction

It was very interesting to observe that tetralogy of Fallot was associated in five of the 17 cases angiographically demonstrated and reviewed by Pieroni and associates[1] If we add another case of right aortic arch isolation of the left subclavian artery and tetralogy of Fallot described anatomically but without roentgenographic features and reported on by Stewart and associates,[5] we can think that the later cardiac anomaly is associated in one third of cases In other respects, tetralogy of Fallot one of the most frequent cyanotic congenital cardiac diseases is associated with a right aortic arch in about 20 per cent of cases realizing the so-called Corvisart syndrome or Caillaud Fallot syndrome in the French literature A systematic research of subclavian steal in this syndrome should be perhaps rewarded by the identification of new cases

From a practical point of view failure to recognize the presence of an isolated or an atretic proximal left subclavian artery in a tetralogy of Fallot may eventuate in a futile attempt at a Blalock Taussig anastomosis

Therefore if a careful examination of both brachial pulses as well as the femorals should be performed routinely in the coarctation of aorta the same management should be a good rule in tetralogy of Fallot or even in a congenital disease

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Books received

Medicine's Metaphors Messages and Menaces By Samuel Vaisrub M D Oradell N J 1977 Medical Economics Company 124 pages Price $7 95

Cardiovascular Nursing Prevention Intervention and Rehabilitation By Jeanne M Holland R N M S *Boston* 1977 Little Brown & Company 218 pages

Principles of Acute Coronary Care By William T Foster M D New York 1977 Appleton Century Crofts 253 pages Price $9 95

Primary and Secondary Raynaud Phenomena Edited by Jan Erik Gjores and Olav Thulesius Stockholm Sweden 19 Almquist and Wiksell International 95 pages Price Swedish krona

Molecular Aspects of Medicine vol 1 No 2 Haemoglobin Structure and Function Its Relevance to Biochemistry and Medicine By *J M White Elmsford N Y 1977 Pergam* Press 184 pages Price $8 00

Announcements

Clinical Application of Intra aortic Balloon Pump course

A three day course on the clinical application of the intra aortic balloon pump will be held on November 25 through 27 1977 (immediately preceding the American Heart Association meeting) at the Konover Hotel Miami Beach Florida Designed for cardiologists, cardiac surgeons anesthesiologists physicians working in intensive care units and for critical care nurses and circulatory assist technicians the course will cover indications for use of the IABP and other circulatory assist devices for patients in cardiogenic shock

The course will be sponsored by the Division of Thoracic and Cardiovascular Surgery and Cardiology University of *Miami School of Medicine For further information regarding* the course please contact Division of Continuing Medical Education University of Miami School of Medicine P O Box 520875 Miami Fla 33152 Telephone (305) 547 6716

Change in the training requirements for the American Board of Internal Medicine s subspecialty examinations

The American Board of Internal Medicine has announced a significant change in policy regarding its training requirements This change will affect physicians desiring admission to a subspecialty examination who began their residency training in *internal medicine* before June 1 1970 At present these physicians are considered to have met the training requirements for admission to a subspecialty examination after completing one year of acceptable training in the subspecialty *If once informed of admission to a subspecialty examination* these physicians *will continue* to be considered to have *fulfilled the Board s training requirements in that subspecialty* Beginning with the subspecialty examination offered in 1981 however *all physicians* not previously admitted to an examination will be required to meet the same training requirements which apply to physicians beginning their residency training after June 1 1970 These requirements currently involved two full years of acceptable training in the subspecialty A complete description of the Board s policies and procedures may be obtained by directing a written request to American Board of Internal Medicine *3930 Chestnut St* Philadelphia PA 19104 The next examination in Cardiovascular *Disease will be offered in June 1979*

Second Pediatric Nephrology symposium

The *Second Pediatric Nephrology* symposium will be sponsored by Georgetown University and the San Juan City Hospital Condado Beach Hotel San Juan Puerto Rico on *December 6 to 9 1977 Topics* will include nephrologic problems of the newborn evaluation of the patient with renal disease treatment of renal disease systemic disease and the kidney renal physiology and dialysis and transplantation Speakers are internationally known in the field of Nephrology Acreditation in Category I for the Physician s Recognition Award has been applied for Tuition $150 for physicians in practice $75 for physicians in training with letter from chief of service For information write *José F Pascual* M D PO Box 3342 Old San Juan Puerto Rico 00904

International Society of Hypertension meeting

The *fifth scientific meeting of the International Society of* Hypertension will be held in Maison de la Chimie Paris on June 12 through 14 1978 Main topics will be *hormones and blood pressure the central nervous system and hypertension transmitters and receptors in hypertension* and hypertension *care For further information regarding this meeting please* contact Professor Paul Milliez Service de Médecine I Hôpital Broussai 96 Rue Didot 75014 Paris France or Professor Philippe Meyer INSERM U 7 Hôpital Necker 161 Rue de Sèvres 75015 Paris France

Cardiopathy of Aging

Cardiopathy of Aging IV *(Heart disease in the elderly patient)* will be presented in Little Rock AR on May 16 and 17 1978 by the Veterans Administration University of Arkansas College of Medicine Council on Clinical Cardiology *of the American Heart Association and the Tri State Scientific Sessions of the American Heart Association Information regarding this symposium may be obtained from* J E Doherty M D Program Director Cardiopathy of Aging IV *300 E Roosevelt Rd Little Rock AR 72206*

Obituary

Thomas M McMillan Jr M D *

1892 1976



Thomas M McMillan Jr died October 17 1976 at the age of 84 in his native and beloved Mobile Alabama He had returned there in 1964 after a long life of devoted professional service in Philadelphia He was a member of the College of Physicians (of Philadelphia) for fifty two years

Tom was born in Mobile Alabama on January 27 1892 His father had served as a youngster in the Confederate Army and was self educated After the war he entered the lumber business running a sawmill and later acquiring large tracts of farm and forest land He had a country plantation in Stockton Alabama where his family spent many happy vacations His mother was an outstanding woman and a very progressive person in the community She was one of the first women to graduate from college started the first library in Mobile and was a leader in the cause of education for Negroes From her Tom received early religious training and exposure to the classics

Tom attended Mr Wright s Military School in Mobile where he played on the baseball team He played the violin and showed an early interest in religious things a preview of what was later to become an important part of his professional and social life An older brother became a Presbyterian Minister He came north to attend Princeton where he received an A B degree in 1913 He was Vice President of his class and manager of the Track Team and was voted the most popular man of his class He was later awarded the class cup and cited for embodying the highest ideals of his profession Tom entered the Medical School of the University of Pennsylvania where he graduated in 1917 He immediately joined the Army Medical Corps as a first Lieutenant and served for a period of two years including an overseas assignment in France On his return to civilian life he spent two years doing special work at the Hospital of the University of Pennsylvania and the Philadelphia General Hospital While in the army he had considered a future career in Surgery or Radiology but in his hospital experience he was greatly influenced by Alfred Stengel and Edward Krumbhaar The latter was one of the first physicians in this country to use the string galvanometer and had published his first paper in that field as early as 1916 He was engaged in functional and pathological studies on the heart at this time Krumbhaar was later to become a life long benefactor of the College of Physicians of Philadelphia and to serve as its President from

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Pratap Reddy
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Michael Reichgott
F W Reynolds Jr
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William Roberts
George Rowe
Carl J Rubenstein
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C Glenn Sawyer
Dante Scarpelli
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E D Wigle
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Travis Winsor
A C Witham
Stephen Wittenberg
Kinsman Wright
Paul Yu
Robert Zelis
Henry Zimmerman
Harry Zinsser
Douglas Zipes

helper There are three children from this devoted couple Thomas M McMillan III a physician and cardiologist in Mt Holly New Jersey and two daughters Frances T Russell (married to a physician) and Mrs Julia I Turnball There are nine grandchildren Harold M Marvin a close friend who followed Tom as the Editor of *Circulation* wrote the following in his preface to the special edition of this journal dedicated to him

The first ten volumes of this journal will stand as a lasting monument to his ability and his consecration to the work that he loved But he has created something else which even though invisible and intangible he may regard as much greater the respect admiration and abiding affection of all who have been privileged to know him His students associates and friends are agreed that few indeed have been blessed with such a rare combination of qualities intelligence and understanding complete sincerity patience and tolerance an unfailing gentleness rarely encountered in men a sweet and happy disposition The years in Philadelphia have taken away none of the consideration for others or the charming graciousness that he brought from his Alabama home His inability to think or speak harshly of anyone has been an inspiration to those who recognize it as strength not weakness as another manifestation of a warm and lovable personality

Thomas McMillan will long be remembered as a refined sensitive cultured gentleman His influence lives on in his many friends and former students

Joseph B Vander Veer M D

1940 to 1943 With this experience young Tom McMillan decided on the field of Medicine and he spent nearly a year in London working in Cardiology and Physiology with Sir Thomas Lewis and *E H Starling*

On his return to this country he began a career of hospital practice teaching, and editorships, seldom equalled to our profession In 1923 he was appointed an Assistant Physician to the Pennsylvania Hospital and to *Physician and Chief of the* Out Patient Department in 1932 In 1946 he was *made head of the Department of Internal Medi*cine and Consultant Cardiologist to the Pennsylvania Hospital He served in the Division of Cardiology at the Philadelphia General Hospital beginning in 1932 and was chief of this Division for many years He was cardiologist and later consultant cardiologist to the Burlington County *(N J) Memorial Hospital He served as a chief* consultant in Cardiology to the Veterans Administration for many years With William D Stroud and others he was active in the formation of the Philadelphia Heart Association in the late 1920s one of the first associations of its kind, later to become affiliated with the American Heart Asso*ciation as the Heart Association of S E Pennsyl*vania He served as its president from 1941 to 1944 He was active in the *Pennsylvania State* Heart Association serving as a Director and was a member of many committees He was one of the Founders of the Childrens Heart Hospital

Tom was a master bedside teacher and his gentle, friendly manner in discussing *patient s* problems on rounds was an example to all His lectures *in Electrocardiography were outstanding* and hundreds of medical and post graduate students received a *practical working knowledge* of this new and important field from his series of lectures, given patiently year after year but always including the newest information in this rapidly growing subject In 1946 despite his many duties he accepted the Editorship of the AMERICAN HEART JOURNAL then the official journal of the American Heart Association He devoted much time to this important task and was so *successful in it that in 1950 when the Heart* Association decided to launch a new official journal, *Circulation* representing its broadening interest from the heart to the entire circulation no one else was even considered *as Editor He* held this position for five years and at the termination of his editorship, a special issue of *Circulation* was dedicated to him He was a director of *the American Heart Association for many years* and received the Gold Heart Award of that Association in 1955

Tom was active in the American College of Physicians serving as Governor for Eastern Pennsylvania *from 1949 to 1958* He was chairman of the Committee on Post Graduate courses of the *College from 1949 to 1953 He was honored by the* College and the Alfred Stengel Award in 1954 and a Mastership in 1964 He was a Regent of the College from 1960 to 1964, and was a Vice President When it was decided to publish a bulletin for the College, he was chosen as its Editor and he served in this capacity from 1960 to 1964

With *all of these professional duties* Tom found time for his family and he had many interests outside of Medicine He was a member of the Session of the First Presbyterian Church of Philadelphia *for many years* and a Trustee of the Princeton Theological Seminary from 1948 to 1967 He also served as a Trustee of Lincoln University

He was a great student of history and an *admirer of Robert E Lee and had many* of his personal effects On his return to Mobile in 1964 *he did not practice Medicine* but his interest in medical affairs did not wane He was an Honorary Consultant in Cardiology to the Mobile General Hospital and an Honorary Member of the Alabama Medical Society He was active in the formation of the new Medical School of South Alabama He attended rounds at the Hospital of *the Medical School* the Providence Hospital and the Mobile Infirmary A physician many years his *junior said 'he was well known respected* and admired by all of the Medical community He was an active member of the Board *of the City* Museum of Mobile

His extensive collection of letters and manuscripts related to the early history of the city of Mobile extended from colonial Mobile under the French through the Revolution and up through Civil War Times It was left to the City Museum *of Mobile*

Thomas McMillan married Julia Talcott of New York City in 1919 They had become acquainted during many visits to her relatives in *Mobile This lovely gracious* lady who survives him was his lifelong companion and ever present

in many ways to improve the regional status of medicine

For years educational administrators have clearly indicated that the quality of teaching was much better when classes were small than when they were large. Today these same administrators need money for their schools. Because the Federal Government will give them money for construction and operation if they increase the size of their classes, they increase their student bodies to levels that were considered unacceptable and inadvisable only a few years ago. If large classes were not ideal several years ago, are they really good today? If so, why? Because of money? There should be no compromise with the *quality* of medical training, scholarship, or service to sick people. If schools need more money, then money should be provided and new schools with *small* classes should be opened. Doctors are concerned with the lives of people, many of whom are the mothers and fathers of young children who need their parents. Remember, children without parents are prone to become delinquent. The treatment of a mother who has four children and a husband is concerned with treatment for the benefit and welfare of *six* people, not one person. The medical schools of today should obtain more financial assistance but not by adding new students to already large classes merely to obtain money when educators truthfully know that small classes are the best. Remember, many of these same educators try to send their own children to the small colleges when possible rather than to large colleges and universities.

Another point for consideration is that the old schools manifest symptoms of senility in many ways. They try to rejuvenate by changing their curricula. The core and elective programs are only attempts to appear youthful and progressive. The results so far have been as successful as the old man who tries to behave as he did in his twenties. New schools provide opportunities for experimentation in faculties, students, organizations, administration, curriculum, building, laboratories, relationships to local hospitals and the community, research in hospital construction and operation, and many other new possibilities. The existing schools find it difficult to make drastic changes because of their many old accumulated commitments. And when they attempt changes the results are poor or even catastrophic. New schools will bring vigor to medical education and provide healthy competition to the older ones.

The U.S.A. needs at least 300 more medical schools opened gradually with small student bodies and eventually high quality faculty from whom scholarship rather than fund raising is expected. There are enough qualified students to fill these additional schools (hundreds of applicants are being rejected annually) and enough faculty to open some schools now, while additional faculty can be trained and accumulated for other schools. Furthermore, the admissions committees need to modify their criteria for admission to the medical schools. The personal integrity, quality and type of motivation, ability to think logically, physical strength and willingness to work hard, and willingness to dedicate oneself to the care of the sick are of primary importance. When the supply of physicians fulfills the demands for service to *all* people, then the doctor supply for rural, urban, and remote areas will be met on a voluntary basis satisfying the "law of supply and demand."

The idea to educate and provide "physicians assistants" to fulfill the need for more doctors is ridiculous. When the airlines need more pilots they do not train more stewardesses to pilot the planes. The financial risk and risk to passenger lives would be too great, and the FAA would not even permit such a plan. On the other hand, the medical organizations and administrators recognize the critical need for highly qualified doctors and yet they allow physicians assistants to replace many of their doctors. Medicine is complex and millions of lives are involved. The release of physician assistants to care for the sick will lead to many difficulties, injury to people, and medico-legal and socioeconomic problems. Furthermore, well-defined and disciplined assistants to physicians already exist in the form of technicians, nurses, aides, and others. The real shortage is a shortage of highly qualified doctors.

It is difficult to understand why many medical schools are reducing the length of time for training in the medical schools when the faculty, students, and administrators readily indicate that medical knowledge is ever expanding. Some even state that "there is too much to learn." This is not a logical argument. This is analogous to saying it requires one week to read the Bible, but

Editorial

The shortage of doctors and new medical schools

G E Burch, M D
New Orleans La

It is generally accepted by everyone, certainly the American people, that America is short of doctors. They learn this when they enter crowded waiting and reception rooms and attempt to make an early or immediate appointment to see the doctor. This crisis had its beginning many years ago and the symptoms are now apparent even to the casual observer. Nevertheless this rapidly developing need and impending crisis was ignored until recently. In haste to supply the U S A with doctors the programs launched revealed relatively poor planning and impulsive decisions. However, with careful consideration of the proposed solutions many useful contributions can be made to the entire welfare of this country and its sick people. A brief discussion of them may be worthwhile.

The U S A is constantly increasing in population therefore the plans should include considerations not only of the immediate needs but also of future requirements to satisfy growth in population and the demands for good careful and thoughtful medical care. Furthermore as much as possible should be derived from the funds personnel and effort presently available. A great deal can be accomplished if the planners are carefully selected and if the only 'selfish' attitude allowed is that concerned with the welfare of the entire U S A and all of its people and not only of selected individuals regions centers and institutions. Remember the strength of America resides in the minds of *all* of its people. No region has a monopoly on intelligence and certain regions are losing their monopoly on knowledge. The vigorous intelligent healthy and highly and properly motivated people must be exploited for the benefit of the entire U S A. Intelligence and the many other excellent attributes of fine and vigorous people are not the monopolies of the rich or of any one select group. The potentials of the less densely populated areas of America need consideration for the future for many obvious reasons. Therefore the training of new doctors should include considerations beyond the obvious objective of merely producing doctors especially since other things can be accomplished simultaneously with the education of doctors. The overpopulated areas need to be depopulated to some extent whereas the small cities, small towns and hamlets can absorb people and profit from the associated cultural and educational developments related to medical education. Therefore why not provide many more medical schools and locate them in areas of America where growth and development should occur to the best advantage of the entire U S A? A medical school with its faculty students staff of secretaries, technicians typists and other supporting corps offers considerable cultural and intellectual advantage to any community regardless of its size or location. The husbands wives and children are also of considerable importance to the life happiness and economy of any community. The medical school and all its medical activities improve the quality of medical practice for miles around. Therefore because of such factors alone we should have more medical schools located in cities and areas where schools do not exist today. This would improve the quality of medicine over a wide region and add to local culture economy and the intellectual atmosphere. The faculty would add to local medical service both as consultants for special problems and for direct service to patients. The local hospitals would improve and the students and faculty could serve

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Propranolol in mitral stenosis during sinus rhythm*

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In mild or moderate mitral stenosis symptoms are typically those of pulmonary congestion due to left atrial and pulmonary venous hypertension Resting cardiac output may be normal and may increase in response to peripheral demand[1] Patients at this stage of the disease are commonly in sinus rhythm and become symptomatic chiefly in situations where heart rate cardiac output or both are substantially increased

Beta adrenergic blocking drugs are capable of lowering both heart rate and cardiac output[2] and might be expected to reduce the diastolic pressure gradient across a stenotic mitral valve thereby reducing pulmonary congestion However the negative inotropic effect of an agent such as propranolol might tend to increase left ventricular diastolic pressures and thereby negate this potentially beneficial effect Several reports documenting the existence of impaired left ventricular function in some patients with mitral stenosis[3-5] lend substance to this concern

Accordingly this study was intended to determine whether propranolol administered acutely to patients with early symptomatic isolated mitral stenosis in sinus rhythm would result in a potentially useful net reduction in pulmonary capillary wedge pressure

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*This study was presented in part t the 24th Annual Scientific Sess on of The American Co eg f C rd logy

Methods

Eight patients with a clinical diagnosis of mitral stenosis who were in sinus rhythm were studied during cardiac catheterization performed to evaluate their need for cardiac surgery All had been experiencing intermittent symptoms of pulmonary congestion All were considered to be in the New York Heart Association (NYHA) status and prognosis class 2 2 None had clinical evidence of severe pulmonary hypertension or right heart failure None had evidence at catheterization of aortic valve disease or more than trivial mitral regurgitation None gave a history of angina pectoris and the four patients who had coronary arteriography had normal coronary arteries Biographical and baseline catheterization data are summarized in Table I

Heart rate pulmonary arterial pressure pulmonary wedge pressure left ventricular systolic and end diastolic pressures as well as Fick or Cardio Green dye dilution cardiac outputs were obtained immediately prior to and ten minutes following intravenous bolus injection of 2 mg of propranolol hydrochloride All measurements were obtained either prior to or at least twenty minutes following angiography utilizing fluid filled catheters and Statham P 23 Db strain gauges Recordings were made at 75 mm /second on an Electronics for Medicine DR 12 amplifier-recorder system Pulmonary wedge pressures were validated by withdrawal of fully arterialized blood from the wedged catheters Mitral diastolic pressure gradients were calculated by planimetry of simultaneously recorded phase corrected equisensitive pulmonary wedge and left ventric

we shall only allow one half week for reading the Bible The result will be that only one half the Bible will be read The U S A is reducing its medical school training to two to three years whereas the more realistic and apparently wiser Russians are increasing their medical training from five to seven years [3] The Russians are also emphasizing quality, scholarly pursuits, and research whereas the U S A is emphasing quantity and rapid rate of production of doctors If these trends continue within the next 10 to 20 years the center of medicine of the world will transfer from the U S A to Russia People will fly to Russia for their surgery diagnosis, treatment and medical evaluation A Russian diploma or certificate will become the premium one rather than the one from the U S A Our present training program is extremely short sighted It needs careful unbiased review and proper attention Medical schools must be supported and not forced to ' earn money '

If we need more doctors, let us train more doctors with a well conceived plan and with the necessary *financial support* and other sacrifices—but *quality* must always prevail

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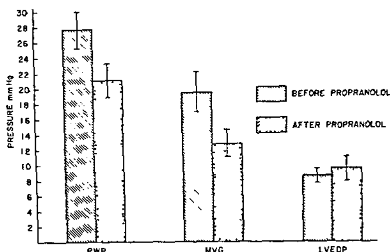


Fig 1 Propranolol induced changes in pulmonary wedge pressure *(PWP)* pressure gradient across the mitral valve *(MVG)* and left ventricular end-diastolic pressure *(LVEDP)* Standard errors of the mean are bracketed

Table II Hemodynamic data pre and post propranolol

	Pre propranolol							*Post propranolol*						
Patient	*PWP*	*PAP*	*LVEDP*	*LVSP*	*CO*	*HR*	*SV*	*PWP*	*PAP*	*LVEDP*	*LVSP*	*CO*	*HR*	*SV*
1 PZ	35	38	10	136	4 4	120	37	21	27	8	1?0	3 9	100	39
? DL	34	60	4	100	3 8	100	38	?7	50	6	98	3 2	78	41
3 JC	24	33	12	108	4 3	8	55	20	30	17	107	4 4	72	61
4 MS	37	7_	9	140	4 0	97	41	31	60	11	142	4 3	86	50
5 EP	25	32	8	15?	6 2	100	6?	15	2?	8	14?	4 8	90	53
6 FW	20	—	6	1?0	3 3	108	31	15	—	5	110	2 6	84	?9
7 ER	20	28	12	133	4 ?	60	0	16	22	13	123	3 6	55	66
8 AM	28	47	8	116	5 4	66	8?	23	36	9	1?2	5 5	60	92
Mean ± SEM	27 9 ± 2 4	44 3 ± 6 2	8 6 ± 1 0	125 6 ± 6?	4 45 ± 0 33	91 1 ± 7 4	5 ± 6 4	21 0 ± 2 1	35 3 ± 5 5	9 6 ± 1 4	1?0 5 ± 5 6	4 04 ± 0 32	?8 1 ± 5 4	53 9 ± 6 9

Abbreviations CO = cardiac output (L/min) HR = heart rate (beat/min) LVEDP = left ventricular end-diastolic pressure (mm Hg) LVSP = left ventricular systolic pressure (mm Hg) PAP = mean pulmonary artery pressure (mm Hg) PWP = pulmonary wedge pressure (mm Hg) SV = stroke volume (cc/beat) SEM = standard error of the mean

suggested a potential therapeutic role for propranolol in selected patients

Conversely Cumming and Carr also observed a reduction in transmitral gradient but concluded that propranolol resulted in an over all reduction in cardiac performance and has no place in the therapy of mitral stenosis This assessment was apparently based on the observation of reduced cardiac output and a rise in left ventricular end diastolic pressure However their patients had a variety of associated cardiac pathologies including mitral and tricuspid insufficiency aortic stenosis coronary artery disease and atrial fibrillation

We did not observe a significant rise in left ventricular end diastolic pressure presumably because our patients were selected to avoid associated pathology likely to impair left ventricular function Since patients with early symptomatic mitral stenosis suffer from pulmonary congestion rather than diminished tissue perfusion small reductions in cardiac output seem acceptable in exchange for a lowered left atrial pressure A similar exchange occurs when diuretics are used in patients with mitral stenosis

The hemodynamic effects observed in this acute study might indeed be useful if achievable on a long term basis with oral propranolol Propranolol therapy is not suggested as a substitute for definitive surgery It might however prove a useful component of medical therapy in those patients for whom surgery is premature or

Table I Clinical and catheterization data

Patient	*Age*	*Sex*	*MVA (cm)*	*LVEF*	*Baseline CI (L /min /M)*
P Z	60	F	0 8	60	2 8
D L	42	F	0 5	–	2 1
J C	44	M	0 9	52	2 4
M S	64	M	0 7	75	2 4
E P	36	F	1 6	68	3 1
F W	43	F	0 8	65	2 2
E R	64	F	0 9	74	2 8
A M	38	F	0 9	–	3 2

Abbreviations MVA = mitral valve area LVEF = left ventricular ejection fraction CI = cardiac index

ular pressure tracings Stroke volume was derived according to the standard formula Mitral valve areas were calculated according to the Gorlin formula using a constant of 38 Statistical comparisons were made with a paired *t* test Changes following propranolol were expressed as mean differences ± standard error of the difference (SED)

Results

Table II lists individual and mean values pre and post propranolol for selected parameters in all patients

As expected significant reductions in both heart rate and cardiac output were observed Heart rate fell by 13 0 beats/min ± 2 6 SED ($p < 0\,005$) Cardiac output fell by 0 5 L/min ± 0 2 ($p < 0\,05$) Stroke volume was unchanged suggesting that the fall in cardiac output was primarily a function of the reduction in heart rate

The mitral diastolic pressure gradient was reduced significantly and in all patients (Fig 1) The mean reduction was 7 1 mm Hg ± 1 6 ($p < 0\,005$) Although several patients had a small rise in left ventricular end diastolic pressure after propranolol there was no significant change for the group as a whole The net reduction in pulmonary wedge pressure was 6 9 mm Hg ± 1 2 ($p < 0\,01$) an average of 25 per cent A commensurate reduction in pulmonary arterial mean pressure—9 0 mm Hg ± 1 2 ($p < 0\,005$) was also seen Fig 2 shows representative simultaneous pulmonary wedge and left ventricular pressure curves before and after propranolol in one patient A borderline significant ($p > 0\,004$ $< 0\,005$) and small (5 1 mm Hg ± 2 6) reduction in left ventricular systolic pressure was observed after propranolol administration The largest reduction in any individual was 16 mm Hg None of the subjects had symptomatic hypotension or bradycardia during the study period or in a subsequent 24 hour observation period

Discussion

The relationship between heart rate cardiac output, and the pressure gradient across stenotic mitral valves was initially described by Gorlin and associates[8] If the mitral valve area formula is solved for the gradient, and if the valve area which does not vary acutely is incorporated in a constant KA the following expression is derived

$$G = \left(\frac{\text{Cardiac output}}{\text{KA} \times \text{diastolic filling period}} \right)^2$$

Thus an increase in cardiac output or a decrease in diastolic filling period results in an exponential rise in gradient Since diastolic filling period (as diastolic seconds per minute) is abbreviated as heart rate increases this equation explains the clinical observation that situations in which heart rate and/or cardiac output are increased commonly precipitate symptomatic intervals particularly in patients whose mitral valve areas approach critical narrowing

When mitral stenosis patients remain in sinus rhythm they can be expected to derive little clinical or hemodynamic benefit from digitalis This agent reduces heart rate only slightly in sinus rhythm and has no demonstrable effect on cardiac output in the absence of superimposed left ventricular failure[9] Diuretics have been shown to reduce pulmonary wedge pressure in patients with mitral stenosis but apparently do so via reduction of cardiac output alone without changing heart rate[10]

Since beta adrenergic blocking drugs depress both heart rate and cardiac output they would be expected to reduce the transmitral pressure gradient and pulmonary wedge pressure in patients with mitral stenosis in sinus rhythm This was in fact observed in all of our patients and has been noted in differing context by others Bhatia and co workers[11] utilizing right heart catheterization only studied the effects of propranolol in four patients with isolated mitral stenosis in sinus rhythm They observed a similar reduction in pulmonary wedge pressure and

Conal anatomy in aortic atresia ventricular septal defect, and normally developed left ventricle

Robert M Freedom M D F R C P (C) F A C C
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When aortic atresia is associated with an intact ventricular septum there is invariably marked underdevelopment of the mitral apparatus and left ventricle[1-5] Rarely a moderate or large inter ventricular communication will be found in the patient with aortic atresia When this occurs the left ventricle will be more fully developed and may even approach normal size[6,7] However rare *these patients* might be candidates for aggressive palliative surgery and subsequent ventriculo aortic reconstitution

Because the pathologic findings in only a few of these patients have been reported we wish to more fully document the morphologic *spectrum* of aortic atresia and ventricular septal defect and to draw attention to abnormalities of conal devel opment observed in some of these patients

Case material

In the Cardiovascular Pathology Registry of The Hospital for Sick Children in Toronto are 148 specimens with aortic atresia Six *of these* (4 *per* cent) had large ventricular septal defects *and* normally developed left ventricle In addition *one* patient was shown by cardiac catheterization and angiocardiography to have aortic *atresia* large ventricular septal defect and a well devel oped left ventricle These seven patients form the basis of this report

Results

There were five males and two females The median age at death was 6 days One patient is alive and doing well at 16 *months* palliative surgery having been performed at seven days of age

All patients had visceroatrial situs solitus concordant D ventricular loops and normally related *great arteries* Aortic valve atresia was present in each patient and when viewed exter *nally* the ascending aorta was very much smaller *than the main* pulmonary artery (Fig 1)

No abnormality of systemic or pulmonary venous return was encountered by any patient *In* four of the six necropsied patients the foramen ovale was obliquely patent In one patient there was *a true* deficiency of septum primum resulting in 1 4 cm diameter fossa ovalis defect (Fig 2) A common atrioventricular canal defect was evi dent in one patient (Fig 3)

In each patient the morphologic right ventricle was both hypertrophied and dilated and except for the patient with the common A V canal defect the tricuspid valve was normal From the right ventricular aspect the ventricular defect involved the conal septum in four of the six necropsied patients (Figs 4 to 6) In one patient the defect was membranous a complete A V canal defect was present in one patient (Fig 3) In the surviving patient selective left ventriculog raphy demonstrated a high probably conal defect (Fig 7*a* and *b*) and retrograde aortography

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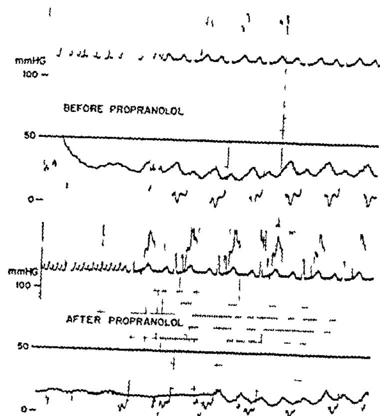


Fig 2 Simultaneous equisensitive left ventricular and pulmonary wedge pressures before and after propranolol in a representative patient *The left portion of each panel* shows mean wedge pressure (paper speed = 10 mm /sec) *The right portion* shows phasic tracings (50 mm /sec)

inadvisable because of associated illnesses It would seem particularly appropriate for mitral stenosis patients with reversible conditions causing increased heart rate cardiac output or both such as fever anemia pregnancy and hyperthyroidism It might also prove useful in areas of the world where the availability of cardiac surgery is limited Its applicability would be limited however to patients with isolated mitral stenosis in sinus rhythm with well maintained cardiac output and no evidence of failure of either ventricle

A longer term study employing oral propranolol in appropriate patients seems justified

Summary

Patients with early symptomatic mitral stenosis usually suffer from pulmonary congestion on the basis of left atrial and pulmonary venous hypertension They are often in sinus rhythm and cardiac output is usually well maintained Symptoms occur most often when heart rate cardiac output or both are increased In this study intravenous propranolol administered to patients with pure mitral stenosis in sinus rhythm resulted in significant reductions in mitral diastolic gradient (−7 1 mm Hg ± 1 6 SED) mean pulmonary wedge pressure (−6 9 mm Hg ± 1 9) and mean pulmonary artery pressures (−9 0 mm Hg ± 1 2) This was due to simultaneous reduction of heart rate (−13 0 beats/minute ± 2 6) and cardiac output (−0 5 L /minute ± 0 2) A small associated reduction of left ventricular systolic pressure (−5 1 mm Hg ± 2 6) was not accompanied by adverse clinical effects A potential role for propranolol in medical management of pure mitral stenosis in the presence of sinus rhythm is suggested

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Conal anatomy in aortic atresia, ventricular septal defect and normally developed left ventricle

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Results

There were five males and two females The median age at death was 6 days One patient is alive and doing well at 16 months palliative surgery having been performed at seven days of age

All patients had visceroatrial situs solitus concordant D ventricular loops and normally related great arteries Aortic valve atresia was present in each patient and when viewed exter nally the ascending aorta was very much smaller than the main pulmonary artery (Fig 1)

No abnormality of systemic or pulmonary venous return was encountered by any patient In four of the six necropsied patients the foramen ovale was obliquely patent In one patient there was a true deficiency of septum primum resulting in 1 4 cm diameter fossa ovalis defect (Fig 2) A common atrioventricular canal defect was evi dent in one patient (Fig 3)

In each patient the morphologic right ventricle was both hypertrophied and dilated and except for the patient with the common A V canal defect the tricuspid valve was normal From the right ventricular aspect the ventricular defect involved the conal septum in four of the six necropsied patients (Figs 4 to 6) In one patient the defect was membranous a complete A V canal defect was present in one patient (Fig 3) In the surviving patient selective left ventriculog raphy demonstrated a high probably conal defect (Fig 7*a* and *b*) and retrograde aortography

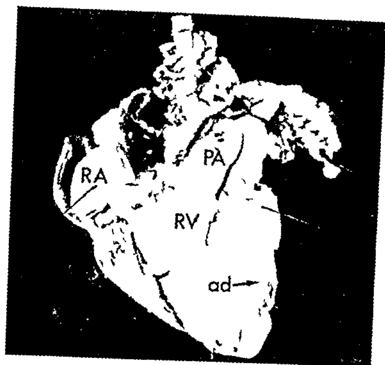


Fig 1 External view of heart in a patient with aortic atresia and normally developed left ventricle This picture is characteristic of the patients in the present study The very large main pulmonary artery *(PA)* is anterior to the much smaller aorta Both right atrium *(RA)* and right ventricle are dilated The epicardial distribution of the anterior descending coronary artery *(ad)* suggests that the cardiac apex is made up of both right and left ventricle Indeed the epicardial course of the anterior descending coronary artery suggests a normally developed left ventricle (Reproduced from Freedom R M Williams W G Dische M R and Rowe R D Anatomic variants in aortic atresia Potential candidates for ventriculo aortic reconstitution Br Heart J 38 821 1976 Reproduced by permission)



Fig 2 Left atrium *(LA)* and ventricle in a patient with aortic atresia and normally developed left ventricle There is a significant secundum atrial septal defect *(arrow)* resulting from deficiency of septum primum The mitral valve *(mv)* appears normal

demonstrated aortic atresia (Fig 8) The muscular ventricular septum was intact in each patient

In the patients with conal defects the ventricular defects were large averaging 1 4 cm in diameter The trabecula septomarginalis was not distorted and the papillary muscle of Lancisi occupied a normal position The conal defect resulted from conoventricular malalignment in three patients (Fig 4) and conal deficiency producing a high intraconal supracristal defect in one patient (Fig 5) Conoventricular malalignment resulted in a leftward deviated conal septum resulting in virtual subaortic atresia In these cases there is characteristic extension of the septal insertion of the conal septum along the craniopostenor edge of the defect into the left ventricle resulting in virtual muscular subaortic atresia above the level of the defect (Figs 9 and 10) In the patient with common atrioventricular canal the abnormal attachment of the mitral component of the common A V valve to the medial border of the left ventricular outflow tract was responsible for virtual subaortic atresia Fibromuscular tissue and accessory cushion tissue resulted in subaortic atresia in the patient with membranous ventricular septal defect In all patients the morphologic left ventricle was both hypertrophied and dilated (Figs 2 3 7 9 to 11) Endocardial fibroelastosis was not identified in any patient

The mitral valve ring averaged 2 6 cm in diameter (excluding the patient with common A V valve) Although the free valve margin of the mitral valve was slightly thickened in two patients functional mitral stenosis was not present in any patient In one of the two patients the chordae tendineae between anterior mitral leaflet and papillary muscle were somewhat shortened possibly resulting in some restriction



Fig 3 Same patient as *Fig 1* Left ventricle *(LV)* in a patient with aortic valve and subvalve atresia and complete common AV canal The subaortic atresia results from anomalous attachment of the mitral component of the common AV valve to the medial aspect of the left ventricular outflow tract *(arrow)* resulting in virtual obliteration of the aortic vestibule (Reproduced from Freedom R M Williams W G Dische M R and Rowe R D Anatomic variants in aortic atresia Potential candidates for ventriculo aortic reconstitution Br Heart J 38 821 1976 Reproduced by permission)

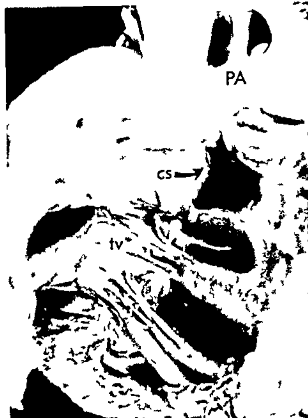


Fig 4 Right ventricle in a patient with aortic atresia and normally developed left ventricle The pulmonary artery originates above this ventricle with pulmonary valve separated from tricuspid valve *(tv)* by conus The large ventricular septal defect results from leftward deviation of the conal septum *(cs)* away from the limbs of the septal band *(curvilinear arrow)*

in the motion of the anterior leaflet of the mitral valve In the six necropsied patients two normally formed left ventricular papillary muscles were evident in each instance

In all patients with aortic atresia and normally developed left ventricle there was membranous as well as subvalve aortic atresia The ascending aorta varied in size from 2 mm to 4 mm in diameter The aortic arch was left sided and in no patient was there significant coarctation The brachiocephalic arteries were normal in origin in each patient and the ductus arteriosus exhibited varying degrees of patency The epicardial distribution of the coronary arteries suggested a normally developed left ventricle in each of the necropsied patients (Fig 1)

Discussion

Despite the presence of a large ventricular septal defect and well developed left ventricle ultimate survival in these patients depends in part on patency of the ductus arteriosus for systemic as well as coronary arterial perfusion Because this entity of aortic atresia VSD and well developed left ventricle is most uncommon clinical recognition depends on (1) awareness of its existence (2) an electrocardiogram which may show more left ventricular forces than typical for the patient with aortic atresia and hypoplasia of the left heart (although rarely left ventricular hypertrophy will be seen in the patient with aortic atresia and diminutive left ventricle) (3) ultrasonography and (4) selective right and left ventriculography and aortography

In an earlier communication we reported the catheter and angiographic findings and the surgical palliation of a patient with aortic atresia large ventricular septal defect and normal left ventricle and suggested that such a patient might be a candidate for ventriculo aortic reconstitution[10, 1] Roberts and colleagues and other workers earlier suggested the same approach suggesting the use of a valved external conduit



Fig 5 Same patient as in *Fig 2* Right ventricle in a patient with aortic atresia and normally developed left ventricle The large pulmonary artery *(PA)* is seen A high intraconal ventricular septal defect *(arrow)* is seen in the immediate subpulmonary (supracristal) position The conal septum *(cs)* is partially deficient The right ventricular free wall *(RFW)* shows considerable hypertrophy The tricuspid valve *(tv)* is shown



Fig 6 Right ventricle in a patient with aortic atresia and normally developed left ventricle The large ventricular septal defect *(arrow)* results from marked conoventricular malalignment The defect lies in the arms of the trabecula septomarginalis *(ts)* The main pulmonary artery *(PA)* is dilated

between left ventricular apex and descending thoracic aorta In the neonatal period short term medical manipulation of the ductus arteriosus might be afforded by prostaglandin infusion This has been shown by Olley and colleagues[14] to result in patency of the ductus arteriosus Formalin infiltration of the ductus arteriosus may provide for ductal patency for some months[14] Finally construction of a surgical anastomosis between aorta and pulmonary artery or insertion of a prosthetic conduit from main pulmonary artery to descending thoracic aorta will ensure continuity between the pulmonary and systemic circulations[15, 16] These procedures will have to be combined with pulmonary artery banding if pulmonary vascular obstructive disease is to be avoided If the patient survives these procedures and does not develop pulmonary vascular obstructive disease then ventriculo aortic reconstitution is a possibility in later childhood[7, 10, 1]

The anatomic type(s) of ventricular septal defect observed in the patient with aortic atresia and normally developed left ventricle resemble those observed in the patient with interruption of the aortic arch[16, 17] Conoventricular malalignment is a common feature of patients with interruption of the aortic arch[18, 19] In 1971 Van Praagh[16] presented the autopsy findings in ten patients with interruption of the aortic arch and suggested that conoventricular malalignment with a leftward shift of the crista supraventricularis, was highly typical for this disorder This conoventricular malalignment and deviation results in a subpulmonary ventricular septal defect and muscular subaortic stenosis We have recently reviewed the conoventricular anatomy in 34 pathologic specimens with interruption of

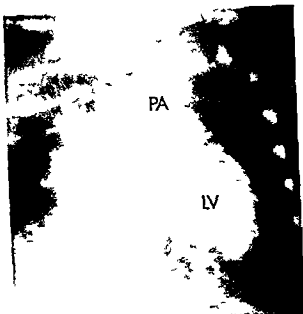


Fig 7A and B Selective left ventricular cineangiocardiograms in the left ventricle with venous catheter having passed through atrial communication and across mitral valve The left ventricle (LV) is of normal size Only the large pulmonary artery (PA) is opacified The ascending aorta is not clearly opacified in these frames (Reproduced from Freedom R M Williams W G Dische M R and Rowe R D Anatomic variants in aortic atresia Potential candidates for ventriculo aortic reconstitution Br Heart J 38 821 1976 Reproduced by permission.)

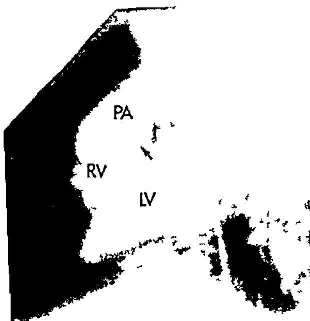


Fig 7B Lateral projection In this projection a high probably conal ventricular defect (arrow) is evident with opacification of the anterior pulmonary artery (PA) and right ventricle (RV) from a left ventricular injection See legend for Fig 7A (Reproduced from Freedom R M Williams W G Dische M R and Rowe R D Anatomic variants in aortic atresia. Potential candidates for ventriculo aortic reconstitution Br Heart J 38 821 1976 Reproduced by permission)

the aortic arch[17] Twenty one patients (all with visceroatrial situs solitus concordant D ventricular loops and two normally related great arteries) had conal ventricular septal defects In 14 of these 21 patients the ventricular septal defect resulted from conoventricular malalignment with leftward deviation of the conal septum allowing actual or potential muscular narrowing of the left ventricular outflow tract (Fig 12) Smaller numbers of patients had intra conal defects without conoventricular malalignment supracristal membranous muscular or canal type defects It is most interesting to note that five of seven patients with aortic atresia and large ventricular septal defects had conal type ventricular septal defects (four at necropsy and one by angiography) In each instance the defect was situated below the leftward deviated conal septum and between the anterior and posterior divisions of the trabecula septomarginalis The conal defects in this group of patients are very similar to the patients with aortic arch interruptions and when viewed from the right ventricular



Fig 8 Selective aortogram performed via the right axillary artery in a patient with aortic atresia and normally developed left ventricle Note the diminutive ascending aorta (arrow) (Reproduced from Freedom R M Williams W G, Dische M R and Rowe R D Anatomic variants in aortic atresia Potential candidates for ventriculo aortic reconstitution Br Heart J 38 821 1976 Reproduced by permission)

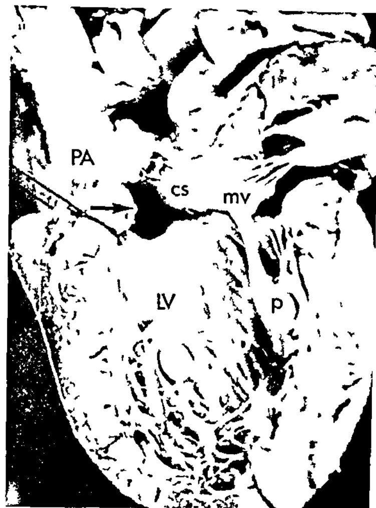


Fig 9 Same patient as in *Fig 6* Left ventricle in a patient with aortic atresia and normally developed left ventricle *(LV)* *The leftward deviated conal septum (cs) virtually occludes the* subaortic area resulting in muscular subvalvular aortic atresia above the ventricular septal defect *(arrow)* *Note the* mitral valve *(mv)* attachment to the conal septum The posterior papillary muscle *(p)* is shown These anatomic features are characteristic of the patient with aortic atresia normally developed left ventricle and the large ventricular defect *(arrow)* resulting from conoventricular malalignment (Reproduced in modified form from Freedom R M Dische *M R* and Rowe R D The pathologic anatomy of subaortic stenosis or atresia in the first year of life Am J Cardiol *(June 1977) Reproduced by permission)*



Fig 10 Same patient as in Fig 4 Left ventricle *(LV) in a* patient with aortic atresia and normally developed left ventricle The large ventricular communication *(arrow)* is shown with a large muscular band above the defect resulting in *muscular subaortic atresia The posterior papillary* muscle of the left ventricle *(p)* is shown

aspect the defects are almost indistinguishable However from the left ventricular view the subaortic area is significantly more distorted in the patient with aortic atresia and large conal ventricular defect than in the patient with aortic arch interruption In the former group the conal septum appears deviated in a significantly more *superior as well as leftward direction virtually* obliterating the subaortic vestibule

The presence of a *significantly restrictive or* minute ventricular septal defect does not allow the patient with aortic atresia to develop a normal left ventricle We have studied several patients with aortic atresia and 1 to 2 mm *ventricular septal defects These patients had* significant underdevelopment of the left ventricle and associated endocardial *fibroelastosis* Certainly then the size of the ventricular defect has a bearing on the developmental status of the *left* ventricle

Disturbances of conal growth and alignment are implicit to the observed morphologic features in tetralogy of Fallot common aorticopulmonary trunk supracristal and/or conal ventricular septal defects the majority of patients with aortic arch interruptions and aortic atresia with normally developed left ventricle Conoventricular *malalignment* and dissociation of the distal conus from the right ventricle are features *shared by the anatomically corrected* malpositions ' Indeed there is a wide spectrum of *congenital cardiac defects in which some* of the most striking anatomic abnormalities reside in



Fig 11 Same patient as in Figs 2 and 5 Left ventricle in a patient with aortic atresia and normally developed left ventricle The large ventricular septal defect is not visible in this projection The left atrium *(LA)* is dilated The mitral valve *(mv)* appears normal with two normally formed papillary muscles *(p)* The left ventricular free wall *(LFW)* is shown The free valve margin of the mitral valve is thin and delicate and the chordae tendineae are not thickened



Fig 12 Right ventricle in a patient with interruption of the aortic arch The ventricular septal defect *(straight arrow)* results from conoventricular malalignment The conal septum *(cs)* is deviated in a leftward direction *(curvilinear arrow)* away from the limbs of the trabecula septomarginalis The pulmonary artery *(PA)* originates above the right ventricle The papillary muscle of the conus *(pc)* is shown Note the similarity of the morphologic features of the conoventricular malalignment in this patient and in the patient with aortic atresia and normally developed left ventricle *(Fig 4)* (Reproduced in modified form from Freedom R M Bain H Esplugas E Dische M R and Rowe R D The ventricular septal defect in interruption of the aortic arch Am J Cardiol 39 5 ? 197? Reproduced by permission)

conal distortions both with normally related great arteries and malpositions and transpositions

In the patient with normally related great arteries conoventricular malalignment with deviation of the conal septum in a leftward or leftward and posterior direction can result in aortic arch interruptions or in aortic atresia with conal ventricular septal defect and normally developed left ventricle When this deviation occurs in a more anterior and rightward direction right ventricular outflow tract obstruction results In 1970 Van Praagh and colleagues suggested that both deviation of the crista supraventricularis and underdevelopment of the infundibulum are the essence of tetralogy This has not been supported by the morphometric and geometric study of Becker and colleagues who suggest that lack of conal inversion and conal malseptation are the morphogenetic mechanisms responsible for the pathologic alterations characteristic of tetralogy of Fallot Furthermore their morphometric measurements indicated that the pulmonary infundibulum was of normal or increased length a view supported by Goor Lillehei and Edwards

The ventricular defects in common aorticopulmonary trunk share some morphologic features with the defects seen in interruption of the aortic arch and aortic atresia with well developed left ventricle The ventricular septal defect

of truncus arteriosus lies between the anterior and posterior limbs of the trabecula septomarginalis and there is either absence or extreme underdevelopment of the parietal band of the crista supraventricularis[21, 3] These defects are conal defects, characterized by deficiency of crista supraventricularis or conal septum As one might anticipate, the supracristal' ventricular septal defect also represents conal deficiency

As stated earlier, the subaortic obstruction seen in some patients with arch interruptions and aortic atresia and normally developed left ventricle results from malalignment of conal septum and trabecula septomarginalis[16, 1] These observations have been recently supported by Moulaert and colleagues[33] In their study of the anomalies of the aortic arch and ventricular septal defects eight of 72 specimens had morphologic features which predisposed to left to right intracardiac shunting In these hearts the ventricular defect was located above the level of the papillary muscle of the conus, and involved the inferior portion of the conal septum In addition, they characterized the ventricular septal defect as resulting from malalignment between conal septum and septal band, and suggested its cardinal feature is extension of the septal insertion of the conus septum along the edge of the defect into the left ventricle obstructing the anterior portion of the left ventricular outflow tract In their eight patients five had arch interruptions one had tubular hypoplasia of the isthmus and one had a juxtaductal coarctation These authors comment that the subaortic stenosis in these patients may sometimes be aggravated by the anterolateral muscle bundle of the left ventricle[34] According to Moulaert and Oppenheimer Dekker,[34] this anterolateral muscle bundle is a muscular remnant of the bulboatrioventricular flange and is present in about 40 per cent of normal hearts preventing normal aortic-mitral fibrous continuity Although the publications of both Van Praagh[16] and Moulaert and colleagues[33, 34] suggest that the ventricular defects typical of aortic arch interruption result from conoventricular malalignment and resulting subaortic stenosis our observations do not entirely support this contention[17] Indeed isolated intraconal defects involving the inferior conal septum, or supracristal (conal) defects constitute a substantial number of the defects associated with aortic interruptions studied in our institution And, in these cases there is not conoventricular malalignment and an obstructing anterolateral muscle bundle was not identified[17] Thus, although it is tempting to suggest that intracardiac anatomic obstruction to the left ventricular outflow tract is responsible for aortic arch anomalies (interruptions, coarctations atresias, etc) by reduction of aortic flow in some specimens there is no morphologic evidence for subaortic narrowing Therefore other mechanisms, such as transitory disturbances of intrauterine intracardiac flow patterns or more focal distortions as the developing aortic arch might be responsible for these anomalies

Although conoventricular malalignment is responsible for the conal ventricular septal defect and obstruction to the subaortic vestibule in the majority of our patients with aortic atresia and normally developed left ventricle this is not invariably the mechanism One patient had a typical membranous ventricular septal defect and yet the subaortic area was plugged with depositions of accessory endocardial cushion tissue In another patient a common A V canal defect was present and the left ventricular outflow tract was virtually obliterated by the marked medial attachment of the mitral component of the common A V valve to the septal surface of the left ventricular outflow tract Numerous reports in the literature have described the anomalous attachment of the mitral valve resulting in subaortic stenosis or atresia[35, 40] Often in these patients, the left ventricle is underdeveloped In this regard aortic atresia and severe underdevelopment of the left heart has been described in a patient with common atrioventricular canal defect[41] Additionally we have studied two pathologic specimens in which aortic atresia was associated with L transposition of the great arteries single left ventricle outlet chamber and two separate A V valves In both patients the bulboventricular foramen was virtually occluded by fibromuscular tissue resulting in subaortic as well as in membranous aortic valve atresia Similarly in those patients with aortic arch interruptions normal conoventricular alignment and subaortic stenosis pathologic mechanisms observed in our patients responsible for narrowing of the aortic vestibule include deposits of accessory endocardial cushion tissue A V canal defects with anomalous attachment of the common A V valve to the medial aspect of the left ventricular outflow tract and fibromuscular diaphragms

Finally although aortic atresia large ventric

ular septal defect and normally developed left ventricle is a most uncommon clinical and pathologic entity increased awareness of its existence and aggressive medical and surgical intervention might provide some hope to this small group of patients

Summary

Although aortic valve atresia is usually associated with severe underdevelopment of the mitral apparatus and left ventricle in rare cases of aortic atresia the left ventricle may be of normal size or even enlarged This occurrence seems related to the presence of a significant ventricular septal defect We have presented the morphologic findings in seven patients with aortic atresia and normally developed left ventricle (six necropsied patients and one studied angiocardiographically) Four autopsied patients had conal type ventricular septal defects characterized in three by conoventricular malalignment Subaortic atresia in these patients resulted from leftward deviation of the conal septum One patient with aortic atresia and well developed left ventricle had a membranous defect and one patient had a complete A V canal The ventricular septal defect in the patients with conoventricular malalignment are very similar to the conal VSD observed in patients with aortic arch interruptions Although ultimate survival with these uncommon groupings of anomalies necessitates patency of the ductus arteriosus clinical recognition rests on (1) awareness of its existence (2) ultrasonography and (3) selective biventricular and aortic angiography It is possible that some of these patients might be candidates for ventriculo aortic reconstitution

Addendum

Subsequent to the submission of this manuscript the one living patient in this series died at 16 months of age some three weeks after the repeat cardiac catheterization Catheterization at 16 months of age revealed the same angiocardiographic features as the initial study with tight bilateral pulmonary bands Necropsy examination revealed a diminutive ascending aorta with membranous valvar and muscular subaortic atresia a large ventricular defect resulting from conal—ventricular septal malalignment a normal mitral valve and a normal left ventricular chamber without endocardial fibroelastosis Tight bilateral pulmonary artery bands were evident The ductus arteriosus remained patent and the surgical anastomosis between aorta and pulmonary artery was 7 5 mm in diameter

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Right parasternal lift in atrial septal defect

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It has been generally accepted that right ventricular overloads produce a palpable impulse in the left parasternal region and that the recording of this amplitude indicates these overloads Previous investigations were concerned only with the left parasternal movement We have recently noticed a characteristic movement in the right parasternal region in patients with atrial septal defect of the secundum type (ASD)

In this paper we describe the right parasternal as well as the left parasternal movement patterns by means of kinetocardiographic methods in patients with secundum ASD We hope to show that the left parasternal lift is as others have conjectured of high amplitude in early systole and the right parasternal lift is of high amplitude in midsystole We also hope to draw attention to the clinical importance of bedside observation of the right and left parasternal lifts in ASD

Material and methods

Fifty two patients with ASD aged 14 to 46 years (18 males and 34 females) were studied (Table I) In all cases the diagnosis of ASD was established by clinical examination chest x ray right cardiac catheterization and selective pulmonary arteriography Pulmonary to systemic flow ratios were measured by the Fick principle

One day prior to cardiac catheterization the impulses at the left and right parasternal regions were examined by kinetocardiography Recordings were obtained in the supine position during expiration using a strain gauge transducer (SB IT Nihon Koden) and a direct writing four channel polygraph (WI 180 Nihon Koden) This recording system has an infinite time constant with a linear response for frequencies of zero to 15 Hz The left and right parasternal impulses were recorded either in the fourth or fifth intercostal space

As a control 30 healthy adults aged 18 to 26 years (12 males and 18 females) were examined by the same procedures In addition six patients with ventricular septal defect (VSD) aged 14 to 24 years five cases with patent ductus arteriosus (PDA) aged 18 to 36 years and eight cases with tricuspid insufficiency combined with mitral stenosis and mitral insufficiency aged 26 to 46 years were examined

Results

Kinetocardiographic tracings obtained from the ASD group and control groups could be divided into four patterns of systolic precordial movement normal hyperkinetic bifid and sustained

The normal and hyperkinetic patterns were characterized by an early systolic outward movement followed by a systolic retraction In the normal pattern the amplitude of the systolic outward movement measured with reference to the presystolic line was smaller than half of the

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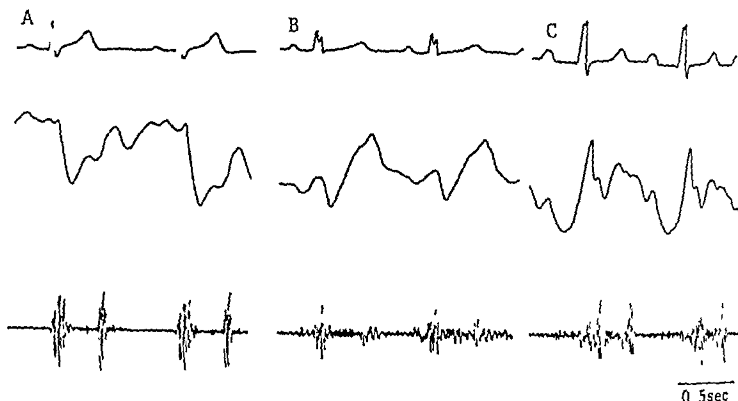


Fig 1 Three basic patterns of the kinetocardiographic tracings classified according to the movement during systole Normal *(A)* Bifid *(B)* and sustained patterns *(C)* are demonstrated in electrocardiogram *(top tracing)* and phonocardiogram *(bottom tracing)*

Table I Incidences of various patterns of kinetocardiographic tracing observed in the healthy and in atrial septal defect (ASD) patients (see text for explanation)

Location examined	*Pattern*	*Healthy subjects*	*ASD subjects*		
		No of cases (%)	*No of cases (%)*	*RVP (mm Hg)*	*Qp/Qs*
Right parasternal region	Normal	30 (100 0)	5 (9 6)	30 6 ± 5 8	1 24 ± 0 30
	Hyperkinetic	0 (0 0)	0 (0 0)	–	–
	Bifid	0 (0 0)	37 (71 2)	39 8 ± 13 5	2 99 ± 0 98
	Sustained	0 (0 0)	10 (19 2)	55 9 ± 31 5	2 85 ± 1 96
Left parasternal region	Normal	25 (83 3)	12 (23 1)	33 0 ± 10 2	1 90 ± 0 73
	Hyperkinetic	5 (16 7)	23 (44 2)	41 2 ± 13 0	3 02 ± 1 09
	Bifid	0 (0 0)	0 (0 0)	–	–
	Sustained	0 (0 0)	17 (32 7)	43 7 ± 25 9	3 14 ± 1 15
	Total	30 (100 0)	52 (100 0)		

Significant at the 0 01 level

total amplitude (Fig 1A) while in the hyperkinetic pattern it was larger than half the total amplitude of the recordings (Fig 2B) In the bifid pattern there was an early systolic outward movement followed by retraction below the base line, and thereafter a dominant midsystolic outward movement with its peak in late systole (Fig 1B and 2A) In the sustained pattern an outward movement continued from early to late systole (Fig 1C)

Table I shows the incidence of each of the four patterns in the control and ASD subjects All healthy subjects showed the normal pattern in the right parasternal region whereas 83 3 per cent showed the normal and 16 7 per cent showed the hyperkinetic patterns in the left parasternal region By contrast, 9 6 per cent 71 2 per cent and 19 2 per cent of ASD patients showed normal bifid and sustained patterns, respectively in the right parasternal region and 23 1 per cent 44 2

per cent and 32.7 per cent showed normal, hyperkinetic, and sustained patterns, respectively, in the left parasternal region. No case of ASD showed a hyperkinetic pattern in the right parasternal region nor a bifid pattern in the left parasternal region.

On the other hand, all cases with VSD and 75 per cent of PDA showed the normal pattern in the left and right parasternal regions (these are not listed in the Table). Almost all of them showed the normal value of right ventricular systolic pressure (mean value ± standard deviation: 24.2 ± 4.2 mm. Hg in VSD, 26.3 ± 5.3 mm. Hg in PDA) and a relatively low pulmonary to systemic flow ratio (1.3 ± 0.6, 1.7 ± 0.3, respectively). A patient suffering from PDA who has high pulmonary to systemic flow ratio (Qp/Qs 3.0) and normal pulmonary artery pressure (26 mm. Hg) showed the bifid pattern in the right and the hyperkinetic pattern in the left parasternal region. All cases with tricuspid insufficiency showed the sustained pattern in the right and left parasternal regions.

The last two columns of Table I give the mean right ventricular systolic pressure (RVP) and pulmonary to systemic flow ratio (Qp/Qs) with their standard deviations for each type of kinetocardiographic patterns observed at the right and left parasternal regions in ASD cases. In the right parasternal region, right ventricular systolic pressure was noted to be highest in the sustained pattern, somewhat lower in the bifid, and lowest in the normal pattern. Qp/Qs was noted to be lower with the normal pattern than with bifid or sustained patterns, showing a significant difference ($P < 0.01$) between normal and bifid patterns. With left parasternal region recordings, both RVP and Qp/Qs were lowest with the normal pattern. No significant difference was noticed in RVP and Qp/Qs in normal, hyperkinetic, and sustained patterns.

Table II gives the incidence of each of the kinetocardiographic patterns among the four groups of ASD. They are subdivided according to values of right ventricular systolic pressure (RVP) and pulmonary to systemic blood flow ratio (Qp/Qs). In the group of low ventricular systolic pressure and low pulmonary flow ($RVP < 50$ mm. Hg, $Qp/Q < 2.0$) the pattern in the right parasternal region was normal in 55.6 per cent and bifid in 44.4 per cent. In two groups

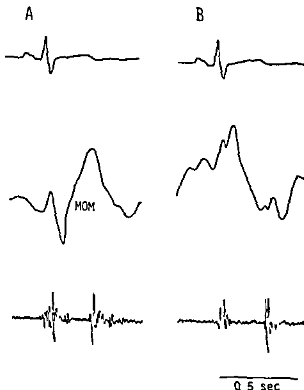


Fig. 2. Tracings from a 26-year-old female patient with ASD (right ventricular systolic pressure, 30 mm. Hg; pulmonic to systemic flow ratio, 2.8). Kinetocardiographic tracings show a *bifid* pattern at the right parasternal region *(A)* and a hyperkinetic pattern movement at the left parasternal region *(B)* in the level at the fifth intercostal space.

with increased pulmonary flow (group of $RVP < 50$ mm. Hg, $Qp/Qs \geqq 2.0$ and that of $RVP \geqq 50$ mm. Hg, $Qp/Qs \geqq 2.0$) the pattern in the right parasternal region was bifid in more than 80 per cent, while none of patients showed a normal pattern. In the group of high right ventricular systolic pressure and low pulmonary flow ($RVP \geqq 50$ mm. Hg, $Qp/Qs < 2.0$), the right parasternal pattern was sustained in 80 per cent.

By contrast, the patterns in the left parasternal region were normal in about 78 per cent of ASD patients with relatively low right ventricular systolic pressure and a low pulmonary flow ($RVP < 50$ mm. Hg, $Qp/Qs < 2.0$). Of 38 cases with increased pulmonary flow ($Qp/Qs \geqq 2.0$), normal, hyperkinetic, and sustained patterns were observed in 10.5 per cent, 55.3 per cent, and 34.2 per cent, respectively. These patterns were also observed in 20 per cent, 40 per cent, and 40 per cent of cases with high right ventricular systolic

Table II Patterns of kinetocardiographic tracings and hemodynamic data of ASD (see text for explanation)

Hemodynamic group		*Right parasternal impulse*			*Left parasternal impulse*			
RVP (mm Hg)	*Qp/Qs*	*No of cases (%)*	*Normal*	*Bifid*	*Sustained*	*Normal*	*Hyperkinetic*	*Sustained*
< 50	< 2.0	9 (100)	5 (55.6)	4 (44.4)	0 (0.0)	7 (77.8)	2 (22.2)	0 (0.0)
< 50	≧ 2.0	32 (100)	0 (0.0)	27 (84.4)	5 (15.6)	4 (12.5)	17 (53.1)	11 (34.4)
≧ 50	≧ 2.0	6 (100)	0 (0.0)	5 (83.3)	1 (16.7)	0 (0.0)	4 (66.7)	[illegible] (33.3)
≧ 50	< 2.0	5 (100)	0 (0.0)	1 (20.0)	4 (80.0)	1 (20.0)	2 (40.0)	[illegible]

pressure and low pulmonary flow (RVP ≧ 50 mm Hg, Qp/Qs < 2.0)

Discussion

It has been reported that ASD tends to show an impulse of a hyperkinetic or a sustained pattern in the left parasternal region. These patterns correspond to the increased pulmonary blood flow ASD and to the high pulmonary resistance ASD, respectively.

In addition, we noted in patients with ASD a right parasternal lift too high in amplitude to be ignored. By kinetocardiographic recording of this lift in the right parasternal fourth intercostal space, the impulse had an early systolic retraction and midsystolic outward movement with its peak at late systole (Figs 1B and 2A). This was named a bifid pattern precordial movement.

The bifid pattern movement in the right parasternal region was observed in 84 per cent of the cases with a high pulmonary flow ASD and 45 per cent of low flow ASD. All normal subjects, 55 per cent of the cases of low flow and low right ventricular systolic pressure ASD, but none with high flow ASD showed the normal pattern. Cases with the bifid pattern movement at the right parasternal region showed a significantly (P < 0.01) higher pulmonary flow than those cases with the normal pattern. The left parasternal movement, however, did not show such a good correlation with hemodynamics as the right parasternal movement. From these findings it may be concluded that the bifid pattern in the kinetocardiographic tracings in the right parasternal region is more useful for characterizing high pulmonary flow ASD than tracings from the left parasternal region.

On the other hand, the sustained pattern in the right parasternal region was observed in 80 per cent of the cases of high right ventricular systolic pressure and low pulmonary flow ASD (high resistance ASD) and in 16 per cent of high pulmonary flow ASD groups. This would seem to reflect pressure overload rather than volume overload in the right ventricle. A similar pattern was observed in cases with mitral valve stenosis associated with pulmonary hypertension.

With regard to other left to right shunt diseases such as ventricular septal defect and patent ductus arteriosus, no definite conclusion can be drawn from this investigation. The only patient with a high pulmonary flow showed the bifid pattern in the right parasternal kinetocardiogram. Almost all other cases with ventricular septal defect and patent ductus arteriosus had small left to right shunt and showed a normal pattern.

In ASD the volume and speed of the right ventricular filling are increased by the shunt flow. The volume ejected in systole is much greater than normal as it includes the shunt flow fraction. The increased volume is expected to increase the speed and amplitude of the right ventricular and pulmonary artery movement,[11] which leads to a high amplitude precordial lift, a bifid pattern movement in the right parasternal region, and a hyperkinetic pattern movement in the left parasternal region. In a relatively low pulmonary flow ASD the right ventricular or pulmonary artery movements are not so increased as to show the bifid pattern.

Tricuspid insufficiency causes rapid and increased right ventricular fillings. It has been reported to produce a systolic retraction in the left and diastolic lift in the right parasternal regions.[1] [1] None of the cases of ASD examined in this study had tricuspid insufficiency and only a few cases of tricuspid insufficiency combined

with mitral valve diseases were examined by this method Even though they were not so typical and severe their right precordial movement patterns were different from the bifid pattern in configuration and in phase

There are only a few reports with respect to the right parasternal impulse of ASD Eddleman and associates only referred to an early systolic outward movement and described the different kinetocardiographic patterns in pressure and volume overloaded right ventricles with specific reference to ASD Although these authors emphasized the systolic retraction in the left parasternal region a midsystolic outward movement was also demonstrated in their right parasternal impulse tracings which corresponds to the bifid wave movement described in this paper

Although kinetocardiographic tracing is very useful in detecting the bifid pattern in the right parasternal region such findings can be detected also by palpation This is accomplished by putting the fingers on the right and left parasternal regions simultaneously The difference in the amplitude and phase of the precordial outward movement in each region can easily be perceived as a reciprocal movement a large outward movement of the early systole in the left parasternal region (impulse of hyperkinetic pattern) followed by an outward movement during midsystole on the right side (impulse of the bifid pattern) (Fig 9)

Summary and conclusion

In 52 cases with atrial septal defect of the ostium secundum type (ASD) and 49 control subjects right and left parasternal impulses were recorded by the kinetocardiographic method These tracings were divided into four patterns according to the systolic movement normal hyperkinetic bifid and sustained

In 30 healthy subjects a normal pattern movement was observed in all cases in the right parasternal region and a normal (83 3 per cent) or a hyperkinetic pattern (16 7 per cent) was seen in the left parasternal region

In cases with ASD normal bifid and sustained patterns were observed in 9 6 per cent 71 2 per cent and 19 2 per cent in the right parasternal region Of 38 ASD cases with increased pulmonary blood flow normal bifid and sustained patterns were observed in 0 per cent 84 2 per cent and 15 8 per cent respectively Of the cases with high right ventricular systolic pressure and low pulmonary flow ASD these patterns were seen in 0 per cent 20 per cent and 80 per cent respectively In the left parasternal region normal hyperkinetic and sustained patterns were observed in 23 1 per cent 45 2 per cent and 32 7 per cent of all ASD cases They were observed in 10 5 per cent 55 3 per cent and 34 2 per cent respectively of the cases with increased pulmonary flow and in 20 per cent 40 per cent and 40 per cent of the cases with high right ventricular systolic pressure and low pulmonary flow

Thus the kinetocardiographic pattern in the right parasternal region showed more intimate correlation with hemodynamic data than that in the left parasternal region

The bifid pattern movement in the right parasternal region was found to be a reliable sign of ASD and was frequently accompanied by the hyperkinetic pattern movement in the left parasternal region These characteristic movements were easily perceived by simultaneously putting two fingers on the right and left parasternal regions

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The length of the left main coronary artery
Pathological features

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The length of the left main coronary artery (L C A) has been diversely estimated in recent pathological and angiographic [3-8] studies In one recent angiographic study a relationship was found between the shortness of the LCA and the presence of stenotic atherosclerotic lesions in the left anterior descending coronary artery (L A D) or the presence of a complete His bundle branch block

This study is purely anatomical and is based on the latest 132 postmortem examinations performed in our Department of Cardiology It aims at clarifying the relation between the length of the LCA and stenotic atherosclerotic lesions in the LAD or a dominant left circumflex coronary artery or a complete His left bundle branch block

Materials

The subjects are the latest 132 postmortem examinations carried out by one of our team (1974 until January 4 1976) They were divided into two groups a first group of cases with evidence of coronary heart disease and a second group of cases with various forms of heart disease without atherosclerotic occlusions of the coronary arteries

1 The 82 cases with evidence of coronary disease included

(a) Twenty six cases with recent lethal myocardial infarction of the anterior wall (patients who died within 30 days of the earliest symptoms) nine men aged 47 to 83 years (average age 64 years) 17 women aged 47 to 93 years (average age 74 years)

(b) Twenty cases with recent lethal myocardial infarction of the posteroinferior wall 11 men aged 44 to 89 years (average age 67 years) nine women aged 66 to 82 years (average age 76 years)

(c) Twenty cases with two or multiple locations of myocardial infarctions eight men aged 39 to 87 years (average age 65 years) 12 women aged 66 to 90 years (average age 77 years)

(d) Sixteen cases with ischemic cardiomyopathies (subendocardial infarctions or extensive myocardial fibrosis) four men aged 55 to 65 years (average age 60 years), 12 women aged 70 to 82 years (average age 76 years)

2 The reference group included 50 postmortem examinations of patients who died of various heart diseases but without significant stenosis of the coronary arteries It contained

(a) Eighteen non obstructive cardiomyopathies 10 men aged 42 to 83 years (average age 64 years) eight women aged 19 to 83 years (average age 56 years)

(b) Fourteen valvular diseases not operated upon 10 aortic (7 men 3 women) aged 38 to 76 years (average age 66 years) four mitral (3 women 1 man) aged 31 to 58 years (average age 45 years)

(c) Fourteen cases with chronic (eight cases) or acute (six cases) thromboembolic cor pulmonale aged 41 to 72 years (average age 62 years)

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Table I Distribution of the 132 cases in relation to the cardiopathy and the average length of the left main coronary artery (see text)*

	Short left main coronary artery	*Long left main coronary artery*	*P value*
C H D (82 cases)	49	33	> 0 05
Miscellaneous (50 cases)	28	22	> 0 05

*Average length of the left main coronary artery = 10 36 mm
C H D = Coronary heart disease (myocardial infarction and ischemic cardiomyopathies)

(d) Four cases with complete heart block aged 71 to 84 years (average age 78 years)

Methods

The details of the postmortem examination were given in previous studies[4] In all cases measurements of the LCA were made (on the artery kept open with scissors) from the ostium to the point of bifurcation into the LAD and left circumflex coronary artery measurements are given in millimeters The mean length of the LCA was calculated from the 132 postmortem examinations 10 36 mm In this study an artery above that mean length will be designated a long LCA and an artery below that mean length will be designated a short LCA (Table I)

Only the significant stenoses (greater than 50 per cent of the arterial lumen) of the LAD were taken into account The atherosclerotic stenoses were divided into short stenoses (< 30 mm) and long stenoses (> 30 mm) In the 82 cases with coronary heart disease the mean length of the LCA was correlated with the heart weight taking into account the extent of the atherosclerotic stenosis of the LAD The results of the data obtained in the study of the 82 cases with coronary heart disease (infarctions ischemic cardiomyopathies) were compared with those obtained in the study of the reference group (50 cases with various forms of heart disease without stenotic atherosclerotic lesions of the coronary arteries)

The relation between the mean length of the LCA and the heart weight was then analyzed by dividing all the cases (coronary heart diseases and various heart diseases) into five groups according to the heart weight (heart weight below 400 Gm between 400 and 499 Gm between 500 and 599 Gm between 600 and 699 Gm and 700 Gm and over)

Finally the length of the LCA was correlated with a dominant left circumflex artery in accordance with criteria defined in a previous study[4] and with a complete His bundle branch block

All the data were analyzed statistically using Student s T test and the χ test with Yates corrections

Table II Mean length of the left main coronary artery and the average weight of the heart in the 82 cases of coronary heart diseases (myocardial infarction or ischemic cardiomyopathy)

	Average length of the left main coronary artery	*Heart weight (average)*
Anterior wall (26 cases)	10 54 mm (6 to 14 mm)	414 Gm (370 to 590 Gm)
Inferior wall (20 cases)	9 85 mm (4 to 15 mm)	413 Gm (300 to 580 Gm)
Anterior inferior and/or lateral walls (20 cases)	10 05 mm (4 to 15 mm)	457 Gm (315 to 610 Gm)
C H D (16 cases)	10 62 mm (6 to 15 mm)	475 Gm (370 to 860 Gm)
Number of cases = 82	10 27 mm	436 Gm

Results

1 Eighty two cases with coronary heart disease The mean length of the LCA was 10 27 mm (ranging from 4 to 15 mm) the mean heart weight was 436 Gm (ranging from 300 to 810 Gm)

When the stenoses of the LAD were short and proximal (43 cases) the mean length of the LCA was 9 90 mm (ranging from 6 to 15 mm), the mean heart weight was 412 Gm (ranging from 300 to 710 Gm) When the stenoses of the LAD were extensive (proximal and distal) the mean length of the LAC was 10 67 mm (ranging from 4 to 15 mm) p > 0 05 the mean heart weight was 462 Gm (ranging from 320 to 810 Gm) p > 0 05 Tables II and III list the results for the whole group and each of the four sub groups

2 Fifty cases with various heart diseases without significant stenosis of the LAD

Table III Specifics of the length of the left main coronary artery and the heart weight in the 82 cases of coronary heart disease in relation to the length of the stenoses of the left anterior descending coronary artery

	Short stenosis		*Long stenosis*	
	L.M C.A	*Heart weight*	*L.M C.A*	*Heart weight*
26 Anterior M I	14 cases 10 44 mm (6 to 14 mm)	14 cases 413 Gm (350 to 540 Gm)	12 cases 10 67 mm (6 to 14 mm)	12 cases 415 Gm (3?0 to 580 Gm)
?0 Inferior M I	11 cases 9 18 mm (6 to 15 mm)	11 cases 383 Gm (300 to 485 Gm)	9 cases 10 67 mm (4 to 15 mm)	9 cases 450 Gm (345 to 580 Gm)
?0 Multiple M I	8 cases 10 25 mm (6 to 12 mm)	8 cases 396 Gm (315 to 5?0 Gm)	12 cases 9 9? mm (4 to 15 mm)	12 cases 498 Gm (360 to 610 Gm)
16 C H. D	10 cases 9 70 mm (6 to 15 mm)	10 cases 455 Gm (3?0 to ?10 Gm)	6 cases 12.17 mm (10 to 15 mm)	6 cases 505 Gm (3 0 to 810 Gm)
Number of cases = 8?	9 90 mm	412 Gm	10 67 mm	462 Gm

M I. = Myocardial infarction L. M C A = l ft main coron ry artery

The mean length of the LCA was 10 52 mm (ranging from 4 to 15 mm) the mean heart weight was 488 Gm (ranging from 285 Gm to 860 Gm) $p > 0.05$ Table IV lists these results

3 The mean length of the LCA was calculated in relation with the heart weight and divided into five groups (see Methods section) In Group I the mean length of the LCA was 9 80 mm (ranging from 6 to 15 mm) the mean heart weight was 351 Gm (ranging from 285 to 395 Gm) In Group II LCA was 10 48 mm (ranging from 4 to 15 mm) heart weight was 439 Gm In Group III LCA was 10 38 mm (ranging from 4 to 14 mm) heart weight was 536 Gm (ranging from 500 to 580 Gm) In Group IV LCA was 11 25 mm (ranging from 8 to 15 mm) heart weight was 628 Gm (ranging from 600 to 695 Gm) In Group V LCA 11 11 mm (ranging from 8 to 14 mm) heart weight 769 Gm (ranging from 710 to 860 Gm) There were no significant statistical differences The results are listed in Table V

4 In 16 cases there was left coronary arterial dominance (the left circumflex vessel giving rise to the posterior descending artery) the 16 cases included three non obstructive cardiomyopathies six coronary heart diseases (infarctions or ischemic cardiomyopathies) and seven valvular heart diseases The mean length of the LCA was 10 75 mm (ranging from 5 to 15 mm) the mean heart weight was 439 Gm (ranging from 390 to 550 Gm) $p > 0.05$

5 In 10 cases there were electrocardiographical patterns of a complete left bundle branch block (in the absence of heart block even of the first degree) The mean length of the LCA was 11 20 mm (ranging from 6 to 16 mm) the mean heart weight was 521 Gm (ranging from 325 to 730 Gm) Because of the limited number of such cases no valid statistical results were available

Discussion

In most cases the LCA rises from the left anterior sinus of Valsalva [4-6] Few pathological or angiographic studies list mean length The figure measured in our study was 10 36 mm—very similar to that reported by Green and associates[3] (11 40 mm) but below that found by Baroldi and Scomazzoni[1] (13 50 mm) and widely different from that found by Fox and colleagues[2] (5 mm) in 100 postmortem examinations of normal hearts The mean length of the LCA found by angiographic studies is very close to our figure 9 5 mm in Fox and colleagues study 10 40 mm in the investigation of Kronzon and associates 12 mm in the study of Furlong and co workers and 12 80 mm in the investigation by Lewis and associates These figures show a striking similarity between pathological and angiographic studies

Contrary to the findings of Fox and colleagues who using both pathological and angiographic determinations found that in 10 per cent of the

Table IV Average length of the left main coronary artery and average weight of the heart in 50 cases of miscellaneous cardiopathies without atherosclerotic stenosis of the coronary arteries (no congenital cardiopathies)

	Average length of the left main coronary artery	*Heart weight*
Non obstructive cardiomyopathies (18 cases)	10 83 mm (4 to 15 mm)	491 Gm (320 to 770 Gm)
C C P and A C P (14 cases)	10 14 mm (6 to 14 mm)	416 Gm (285 to 615 Gm)
Valvular heart diseases (14 cases)	10 29 mm (5 to 14 mm)	569 Gm (340 to 840 Gm)
Complete heart block (4 cases)	11 25 mm (9 to 15 mm)	454 Gm (390 to 560 Gm)
Number of cases = 50	10 52 mm	488 Gm

C C P = chronic cor pulmonale A C P = acute cor pulmonale

Table V Average length of the main coronary artery in relation to the heart weight (see text)

	Average length of the left main coronary artery	*Heart weight*
< 400 Gm (49 cases)	9 80 mm (6 to 15 mm)	351 Gm (285 to 395 Gm)
400 to 499 Gm (49 cases)	10 48 mm (4 to 15 mm)	439 Gm (400 to 495 Gm)
500 to 599 Gm (21 cases)	10 38 mm (4 to 14 mm)	536 Gm (500 to 590 Gm)
600 to 699 Gm (4 cases)	11 25 mm (8 to 15 mm)	628 Gm (600 to 695 Gm)
≥ 700 Gm (9 cases)	11 11 mm (8 to 14 mm)	769 Gm (710 to 860 Gm)

former and in 18 per cent of the latter there was an immediate bifurcation of the LCA our study indicated that the shortest vessel was 4 mm which is in agreement with the findings of Furlong and colleagues

In contrast to the findings of Gazetopoulos and associates based on angiographic assessments our purely anatomical study shows that there is no evidence of a relationship between a short LCA and the presence of stenotic atherosclerosis in the left anterior descending artery It must be pointed out however that the LCA was slightly longer but not significantly so when there were extensive stenoses of the LAD

This study demonstrates that there is almost no relationship between the length of the LCA and heart weight The only point to be noted is that the LCA is slightly longer when the heart is enlarged which is in perfect agreement with the findings of Green and associates[3] and Fox and colleagues (pathological assessments) and with those of Fox and associates Furlong and co workers and Gazetopoulos and colleagues[6] for angiographic investigations

Using angiographic investigations Kronzon and colleagues[7] showed a significant relationship between a short LCA and a dominant left circumflex artery Our anatomical observations do not support this view indeed when the left circumflex artery was dominant (12 per cent of the cases) the mean length of the LCA (in 16 cases) was 10 75 mm, which was not markedly different from the mean length of the same artery when the coronary circulation was balanced or when the right coronary artery was dominant (10 31 mm)

Using angiographic investigations, Gazetopoulos and associates and Lewis and colleagues found a relationship between a short LCA and a complete left bundle branch block Hamby and co workers[11] only report this relationship in 25 per cent of the cases observed Our pathological study seems to demonstrate that there is no significant relationship between a short LCA and a complete left bundle branch block

Summary

The mean length of the LCA found by pathological (or angiographic) methods is fairly constant This exclusively anatomical study shows no significant relationship between the length of the LCA and stenotic atherosclerosis in the LCA or the heart weight or a dominant left circumflex coronary artery or a complete His left bundle branch block

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Clinical study of "A waves" (atrial waves) in impedance cardiograms

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Application of a high frequency sinusoidal current across the chest produces changes in thoracic impedance which can be recorded Kubicek and co workers[1] have proposed a method using these changes to calculate cardiac output which has been termed 'impedance cardiography' As their method allows hemodynamics to be observed noninvasively and continuously it has many clinical applications However, very little is known about the significance of the impedance change waveform as it is quite complex

Two waveforms which usually appear on the impedance cardiogram preceding the ventricular ejection wave have been named the 'A wave and B wave' by Lababidi and colleagues[2] It has been reported that the A wave appears following the P wave of the electrocardiogram (ECG)[2,3] but no experiments studying the A wave quantitatively have been performed

In this study correlations between the A wave and left atrial pressure, volume and volume change, which were calculated from diagnostic cardiac catheterization were examined The effect of various types of arrhythmia and other types of cardiac disorders on the A wave were investigated quantitatively

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Materials and methods

Thoracic impedance data were obtained using an impedance cardiograph* with four disposable aluminized strip electrodes Two strip electrodes encircled the neck and two the upper abdomen one at the level of the xyphoid, the other around the abdomen approximately 3 cm below The outer electrodes provided an electrical field from a constant current oscillator generating a constant sinusoidal current of 350 μA r m s with a frequency of 50 KHz The impedance change was measured between the two inner electrodes

The impedance change waveform (ΔZ wave) and its first derivative (dZ/dt wave) were recorded on a 4 channel ink jet recorder† at a paper speed of 50 mm per second while the subjects were holding their respiration at the end of expiration Lead II of the ECG and the phonocardiogram (PCG) were recorded simultaneously The magnitude from the point of onset of the A wave to the maximal point (the bottom) in A dZ/dt wave was established as A dZ/dt max (Fig 1)

Recordings of the impedance cardiogram were made on 154 cases of sinus rhythm of these 45 were normal young adults, 23 had neurocirculatory asthenia (NCA) 72 had ischemic heart disease (IHD) and 14 had mitral valve disease (MVD) Right cardiac catheterization studies were done on 24 cases of these three were normal young adults six had NCA and 15 had IHD and

*Type RGA 5b Nihon Kohden Co Ltd Tokyo Japan
†Mingograph 34 Elema Schönander Co Ltd Solna Sweden

on all these 24 angiography from the main pulmonary artery was done Filming of the left atrium was performed by rapid serial roentgenography using a biplane rapid film changer (6 plates per second) and the left atrial volume was calculated by the method of Santer and co workers The maximal left atrial volume was calculated at the ventricular end systolic phase which was decided using the end of the T wave of the ECG recorded simultaneously and the minimal volume was decided using the Q wave of the ECG

Recordings were also done on 27 cases of arrhythmia of these 12 were cases of atrial fibrillation four of complete atrioventricular block of which two were paced artificially 10 of first degree atrioventricular block and one case of sick sinus syndrome

The change of the impedance cardiogram and blood pressure before and after administration of isoproterenol (0 01 mg /Kg /min) on one case of complete AV block paced artificially and one case of sick sinus syndrome were also observed

All 136 cases of cardiac disorder were in functional class I or II according to the New York Heart Association criteria

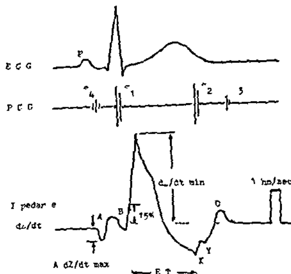


Fig 1 Normal sinus rhythm impedance cardiogram showing the shape of the dZ/dt wave The labeling of the various parts of the dZ/dt wave the correlation with the cardiac phase and the method of measuring A dZ/dt max shown Decreasing impedance results in an upward deflection "A" appears 40 to 100 msec after the P wave of the ECG and "B coincides with the main portion of the first heart sound X usually coincides with the aortic component of the second heart sound and Y O" and Z appear during the rapid filling phase The left ventricular ejection time (ET) may be measured as shown in the figure

Results

In the ΔZ and dZ/dt waveforms appearing in the typical impedance cardiogram of a case of normal sinus rhythm shown in Fig 2 there was an increase in impedance (downward deflection) after the P wave of the ECG followed immediately by a very small wave which appeared together with the main portion of the first heart sound and shifted towards the ventricular ejection wave (Fig 2) It is difficult to examine these waves individually in the ΔZ waveforms as these waves occur without interruption but they can be distinguished into A dZ/dt B dZ/dt and "dZ/dt min through examination of the dZ/dt waveform

In the impedance cardiograms of the 12 cases of atrial fibrillation only the B wave occurring together with the first heart sound could be detected immediately preceding dZ/dt min the A wave could not be detected (Fig 3) The B wave showed a tendency to become larger as the preceding RR interval became shorter

The A wave always appeared 40 to 100 msec after the P wave of the ECG in cases of sinus rhythm and first degree or complete AV block (Figs 4 and 5) Comparing A dZ/dt max with the mean pulmonary block arterial wedge pressure and left atrial volume estimated by cardiac catheterization showed a small correlation with the mean PA wedge pressure ($r = +0.47$ $p < 0.05$) but no correlation with maximum left atrial volume (Fig 6) Comparison of A dZ/dt max with the left atrial ejection fraction (LA vol max – LA vol min)/LA vol max showed extremely high correlation ($r = +0.91$ $p < 0.005$) (Fig 7)

In the cases of complete AV block the relationship between A dZ dt max and the interval between the aortic component of the second heart sound and the P wave of the ECG (S_2 P interval) was also investigated Because of the interference of dZ/dt min and X Y O and Z as shown in Fig 1 A dZ/dt max could not be measured reliably in the ventricular contraction phase or the rapid filling phase However the A dZ/dt max occurring in the slow filling phase in each of the four cases of complete AV block (two of which were paced artificially) tended to become smaller as the S P interval became longer Moreover the relation between the value of A dZ/dt max as compared to that of the S_2 P interval was

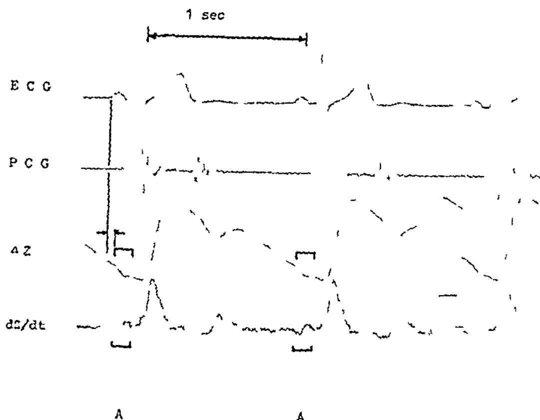


Fig 2 Typical normal sinus rhythm impedance change waveform Tracings shown are from top to bottom Lead II of the ECG the PCG the ΔZ wave and the dZ/dt wave The cone shaped downward deflection of the A wave occurring in the ΔZ wave 40 msec after the P wave of the ECG is extremely small

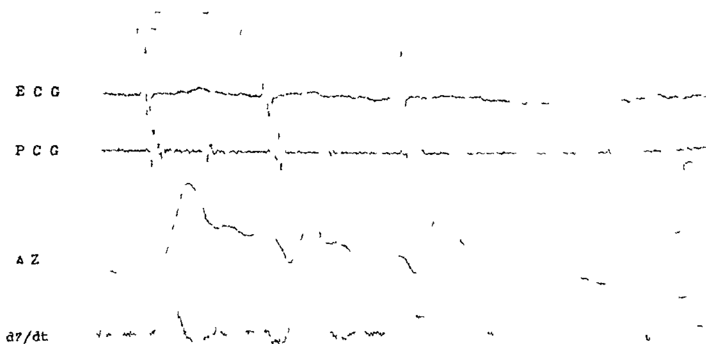


Fig 3 Atrial fibrillation impedance change waveform In atrial fibrillation the A wave is entirely absent and only the B wave occurs coincident with the main portion of the first heart sound B dZ/dt max increases with the decrease of the preceding RR interval

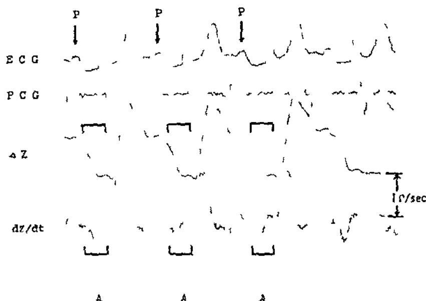


Fig 4 First degree atrioventricular block impedance cardiogram As the PQ interval is extended the A wave may be seen clearly by analyzing the impedance change waveform from the ventricular ejection phase The A wave in the ΔZ wave takes a conical shape showing increasing impedance (downward deflection) 70 msec after the P wave of the ECG

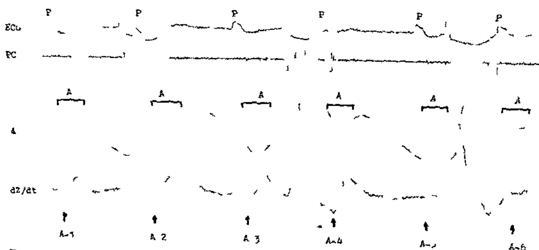


Fig 5 Complete atrioventricular block impedance cardiogram The conically shaped A wave appears in the ΔZ wave 100 msec following the P wave of the ECG Because they are superimposed on other waveforms, the A dZ/dt max of the A waves which occur in the ventricular ejection phase (A 2) and the rapid filling phase (A-4 A 6) are difficult to measure accurately The A dZ/dt max of A waves which occur in the slow filling phase (A 1 A 3 A-4) on the other hand become larger as the preceding P interval becomes shorter (i.e as the PQ interval becomes longer)

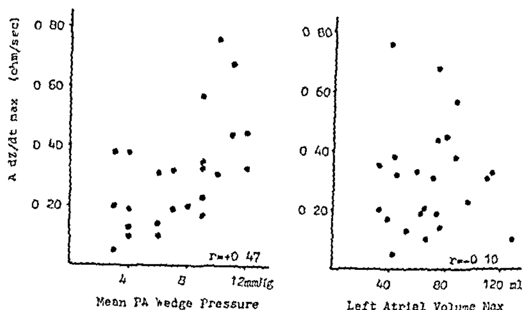


Fig 6 The relationship between A dZ/dt max and mean pulmonary artery wedge pressure *(left)* and maximum left atrial volume *(right)* The ordinates show the values of A dZ/dt max in ohm/sec and the abscissae show mean pulmonary artery wedge pressure in mm Hg *(left)* and maximum left atrial volume in ml *(right)* as measured through cardiac catheterization A significant correlation (r = 0 47 p < 0 05) was found between A dZ/dt max and the mean pulmonary artery wedge pressure but no significant correlation was found between A dZ/dt max and the maximum left atrial volume

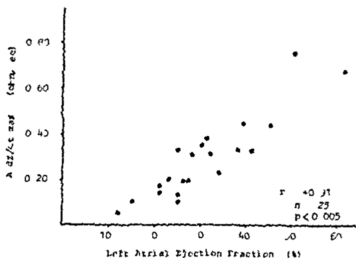


Fig 7 The relationship between A dZ/dt max and the left atrial ejection fraction The left atrial ejection fraction calculated from the maximum left atrial volume (LA vol max) and the minimum left atrial volume (LA vol min) both measured by angiography as follows Left atrial ejection fraction = (LA vol max − LA vol min)/LA vol max × 100 (%) The ordinate shows A dZ/dt max in ohm/sec and the abscissa shows the left atrial ejection fraction in per cent An extremely high correlation (r = 0 91 p < 0 005) was found between A dZ/dt max and the left atrial ejection fraction

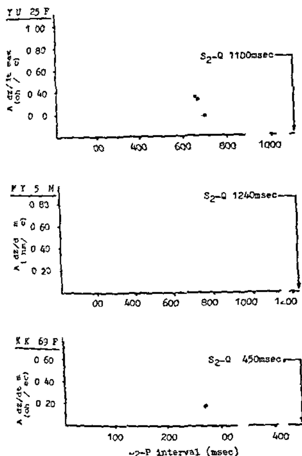
extremely constant over repeated testing (Figs 8 and 9)

Isoproterenol was administrated to one case of sick sinus syndrome (SSS) in which the heart rate fails to respond to administration of various drugs with positive chronotropic effect or exercise and to one of the artificially paced cases mentioned above In the SSS case although the heart rate did not change after two minutes of administration, the blood pressure rose from 140/78 mm Hg to 160/90 mm Hg Accompanying this increase A dZ/dt max increased from 0 45 ohm/sec to 0 65 ohm/sec The paced case also showed a clear increase in A dZ/dt max, as shown in Fig 9

Comparison of A dZ/dt max across the various types of cases showed the following results normal young adults 0 12 ± 0 09 ohm/sec, NCA, 0 30 ± 0 19 ohm/sec, IHD, 0 32 ± 0 18 ohm/sec MVD, 0 46 ± 0 19 ohm/sec The NCA IHD, and MVD cases all showed a significantly (p < 0 05) higher value than the normal young adults Compared to these normal sinus rhythm cases the cases of first degree AV block showed the strikingly higher value of 0 56 ± 0 16 ohm/sec (Fig 10)

Discussion

The thoracic impedance as measured by the application of a high frequency sinusoidal current across the chest has been known since 1932 to decrease concurrent with the ventricular ejection of blood[5] In 1964 Nakagawa and co workers[6] reported that the impedance increases with the atrial contraction as well In impedance cardiograms recorded using Kubicek s method



Fg 8 The relationship between A dZ/dt max and the S P interval in cases of complete atrioventricular block The ordinates indicate A dZ/dt max in ohm/sec and the abscissae the total diastolic interval (the S Q interval) The abscissae are scaled so that the S Q interval in each case will be the same length A close negative correlation was observed between A dZ/dt max and the S P interval in all three cases The case shown at the bottom is artificially paced

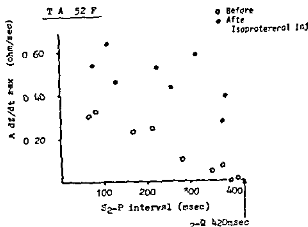


Fig 9 A dZ/dt max before and after isoproterenol administration in an artificially paced case of complete atrioventricular block *The open circles* show the values taken before medication and *the filled circles* show the values after medication A dZ/dt max is shown on the vertical scale in ohm/sec and the S P interval is shown horizontally in msec In both sets of measurements, a negative correlation is observed between A dZ/dt max and S P interval the measured values for A dZ/dt max are clearly higher following medication

appear two prominent preejection waves referred to as the A and B waves The A wave is entirely absent in cases of atrial fibrillation and appears 40 to 100 msec after the P wave of the ECG in cases of sinus rhythm and first degree or complete AV block, as was also reported by Lababidi and colleagues [2] and by Karnegis and Kubicek [3] They recognized that the A wave must originate in blood flow in the venae cavae or the pulmonary artery and suggested that it may be caused by slowing or a brief reversal of this flow However from the fact that the A wave appears at the time of the active atrial contraction and the fact that the B wave is coincident with the ventricular isometric contraction it may be hypothesized that the origin of the A wave is closely connected with the change of volume occurring due to the active atrial contraction

The importance of left atrial function in the left cardiac function has been reported by many reporters and the following noninvasive indicators of left atrial function or left atrial load have been reported (1) The waveform of the P wave as measured ECG[7] or VCG [8] (2) the Q S interval [9] (3) the a wave as measured by an apexcardiogram [10] and (4) the preejection waves appearing in a carotidgram [1] In comparison to these which can be used to estimate only the left atrial pressure or volume the A dZ/dt max allows estimation of left atrial volume change and left atrial contractility since an extremely high correlation was found between the left atrial ejection fraction and A dZ/dt max

The atrium exhibits a volume change in both active and passive contraction In this study it was difficult to observe only active contraction Two mechanisms may be considered for left atrial contractility the Frank Starling effect in the left atrium and accelerated contractility of the muscles of the left atrium themselves The relation between the S P interval and A dZ/dt max in cases of complete AV block indicates that when active contraction occurs in early diastole although the inflow to the ventricle is still insuffi

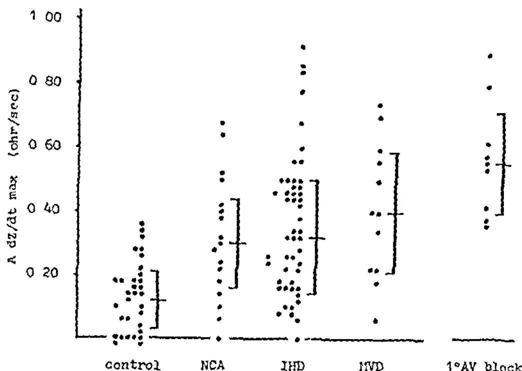


Fig 10 Measured value of A dZ/dt max divided by patient class A dZ/dt max is shown on the ordinate in ohm/sec *The vertical bars* indicate the standard deviation for each group and *the horizontal strike* indicates the mean The value of A dZ/dt max measured in cases of neurocirculatory asthenia (*NCA*) ischemic heart disease (*IHD*) and mitral valve disease (*MVD*) exceed those measured in normal young adults (*control*) by a significant ($p < 0.05$) amount If the normal range of A dZ/dt max is regarded as 0 to 0 35 ohm/sec then 38 per cent (nine cases) of the NCA group 40 per cent (29 cases) of the IHD group and 57 per cent (eight cases) of the MVD group show values which exceed that range In addition the cases in the first degree AV block group exhibit extremely high values compared with those of cases having normal sinus rhythm and all cases in this group show higher values than the normal range

cient and the atrial volume is still large contraction is due to increased atrial contractility or atrial pump function On the other hand the increase of A dZ/dt max in cases where administration of isoproterenol has caused a rise in blood pressure without a corresponding increase in the heart rate is probably the result of an increase in the contractility of the muscles of the atrium themselves

The low value of A dZ/dt max in the normal young adults at rest shows that the blood flow from the atrium to the ventricle in normal cardiac function is satisfactorily accomplished by passive atrial contractions due to the pressure gradient between the atrium and the ventricle and that active atrial contractions have a very little role in the process In contrast in the NCA cases which were characterized by normal cardiac function but a high A dZ/dt max it is suspected that the enhanced atrial contractility is due to autonomic imbalance consisting of stimulation of the sympathetic nervous system and/or inhibition of the vagal nervous system The reason for the large number of IHD cases in which A dZ/dt max is high is probably that the increased load for filling the left atrium is caused by the elevation of the left ventricular end diastolic pressure and/or volume accompanying left ventricular functional derangement Rahimtoola and co workers' obtained similar results from cineangiograms of patients with myocardial infarction and reported on the importance of the booster pump function of the atrium The higher value for A dZ/dt max shown by MVD cases compared with IHD cases is probably to be explained by the higher left atrial load occasioned by MVD

In contrast to these cases which exhibit normal sinus rhythm the strikingly high value of A dZ/dt max observed in cases of first degree AV block may be due to the fact that the active atrial contraction phase has been lengthened and in comparison with cases of normal sinus rhythm active atrial contraction occurs earlier in the diastolic phase even at the same heart rate

In the above results and discussion it has been shown that A dZ/dt max is a noninvasive indi

cator of atrial booster pump function and that it is capable of reflecting even a small change of atrial contractility

Summary

In impedance cardiograms taken by Kubicek's method[1] two preejection waves (the A wave and B wave) are seen. This study is concerned with various aspects of the A wave and the information it contains.

From the fact that the A wave never occurs during atrial fibrillation but always appears following the P wave of the ECG in cases of sinus rhythm and first degree or complete atrioventricular block and that an impedance change occurs during the ventricular isometric contraction phase it may be seen that the impedance change represented by the A wave arises from volume changes due to the active atrial contraction.

The maximum value of the first derivative of the A wave (A dZ/dt max) was found not to correlate with the maximum left atrial volume but to correlate to a small degree ($r = 0.47$, $p < 0.05$) with the mean pulmonary artery wedge pressure and to a high degree ($r = 0.91$, $p < 0.005$) with the left atrial contraction rate. These facts lead to the conclusion that A dZ/dt max may be a noninvasive indicator of atrial contractility.

Using this indicator it was possible to investigate changes in atrial contractility arising from the Frank Starling effect and from the increased contractility of the atrial muscles themselves in cases of complete AV block and sick sinus syndrome.

Concerning the difference of A dZ/dt max found in different classes of patients it was found that it is lowest in normal young adults and higher in IHD and MVD cases in which the left atrial load has been increased. Finally results were obtained which indicate that the high value of A dZ/dt max found in many cases of NCA is caused by increased atrial contractility due to autonomic imbalance.

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Ventricular arrhythmia 24 hours before and after maximal treadmill testing

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Pio F Poblete M D
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Baltimore Md

Maximal exercise treadmill testing is a useful clinical investigative procedure associated with *minimal adverse effects* The effects of exercise testing on aggravating inducing, or suppressing ventricular arrhythmia are of current interest[1-4] These observations have been limited to relatively brief control periods before exercise, periods during exercise, and recovery periods after exercise Prolonged observation of dysrhythmia fol*lowing the post exercise period have* not been previously reported

Frequently cardiac patients are studied by exercise testing and long term electrocardiographic monitoring within the same 24 hour period It is of practical interest to determine if maximal exercise treadmill testing influences *ventricular arrhythmia in the hours following* exercise Accordingly this study examined and compared the quantitative and qualitative aspects of ventricular arrhythmia detected 24 hours before and 24 hours after maximal exercise *treadmill testing employing long term ambula*tory Holter recordings This report details the results of those comparisons

Materials and methods

Subjects Volunteers with ischemic heart disease (67) and normal subjects (23) were selected for this study The diagnosis of ischemic heart disease was based on a previous history of a well documented myocardial infarction in 45 patients and a history of typical attacks of angina pectoris with a positive ischemic ST segment response during exercise treadmill testing in 22 patients An ischemic ST segment response was defined as at least 1 mm of J point depression with a horizontal or downward slope for 0 08 sec Patients with recent myocardial infarction (3 months old or less) and those with unstable angina were excluded from the study Patients were assigned to the myocardial infarction group when the diagnosis of old myocardial infarction with or without angina pectoris was established and to the angina pectoris group when only angina pectoris was present without a *history or evidence of old myocardial infarction* Normal subjects were recruited from the Health Evaluation Clinic of the United States Public Health Service Hospital of Baltimore Maryland All patients volunteered for two consecutive 24 *hour periods of continuous examination* by Holter recording, and engaged in fully ambulatory activities of comparable degree during both days of examination

Table I shows the clinical characteristics of 90 consecutive patients examined who had technically adequate Holter recordings of at least 20 hours duration before and after exercise testing The mean age of the group with ischemic heart disease was 57 years (ranging from 40 to 78 years) The relative age distribution of the patients with myocardial infarction and angina pectoris was comparable Sixty per cent (27 of 45) of myocardial infarction patients had angina pectoris Only seven patients were receiving cardiotropic drugs

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Table I Clinical characteristics of patients

	Total patients	Sex M/F	Mean age (yrs)	Age (yrs)				NYHA Class			Medications	
				35-45	46-55	56-65	66+	0	I II	III IV	Digitalis	Anti-arrhythmic
Myocardial infarction	45	40/5	58 ± 9	4	12	22	7	0	44	1	6	5
Angina pectoris	22	19/3	56 ± 8	2	6	12	2	0	22	0	0	1
Normal	23	22/1	48 ± 9	10	9	4	0	23	0	0	0	0

five patients receiving both digitalis and an antiarrhythmic drug

Holter recording procedure All patients had continuous electrocardiographic recordings obtained for approximately 48 hours by means of a two channel Model 425 Avionics Holter recorder Patients were connected to the recording apparatus 24 hours prior to exercise testing with standard non disposable silver silver chloride electrodes utilizing a modified chest Lead V and chest bipolar Lead V A chronological diary of all physical physiological and emotional events was kept by all patients to insure comparable activities during the two day examination period of Holter recording Analysis of the electrocardiographic Holter recordings was accomplished with the Model 660 Avionics Electrocardioscanner with methodology previously detailed These methods have defined a high speed analysis accuracy of 80 per cent for cumulative quantitative frequency and 85 per cent for recognition of qualitative types of ventricular ectopy when compared to random one hour real time printout sample evaluations Reliability or repeatability has been found to be 84 per cent for quantitative frequency and 80 per cent for qualitative recognition of ventricular ectopy Quantitative frequency of ventricular ectopy was reported as cumulative ventricular ectopic beats per hour and qualitative types of ventricular ectopy were described according to Lown and Wolf[6] as Grade 0 absence of ventricular ectopy Grade 1 less than two ventricular ectopic beats per minute or 30 per hour Grade 2 two or more ventricular ectopic beats per minute or greater than 30 per hour Grade 3 multiform ventricular ectopic beats *Grade 4A* couplets of ventricular ectopic beats Grade 4B three or more consecutive ventricular ectopic beats and Grade 5 early cycle ventricular ectopic beats with R on T phenomenon

Avionics Biomedical Division Del Mar Avionics Irvine Calif

Exercise treadmill testing All subjects had a clinical examination and a resting standard electrocardiogram performed before exercise testing A three minute control period preceded exercise during which a continuous electrocardiographic record was obtained The exercise procedure utilized the Bruce protocol and was simultaneously recorded on an electrocardiographic recorder and by Holter recording The endpoint for exercise was determined by the patient when disabling angina chest pain fatigue dyspnea leg weakness or dizziness occurred The medical supervisor could terminate the procedure if ataxic gait hypotension ST segment depression of 5 mm or more or the emergence of three or more successive ventricular ectopic beats were observed Immediately upon completion of exercise the patient sat in a chair and was instructed to repeatedly plantar flex his feet Electrocardiographic rhythm was continuously recorded for the ensuing three minutes and one minute electrocardiographic samples plus any ventricular ectopy were recorded thereafter The exercise test period was arbitrarily designated as including the three minute control period the exercise period and the recovery period The end of the recovery period was defined by the return of the ST segment heart rate and the occurrence of ventricular ectopy to the same quantitative frequency and qualitative grade observed in the control period This time interval most commonly ranged from five to ten minutes Exercise variables measured included duration of exercise heart rate, blood pressure subjective symptoms ST segment changes and ventricular arrhythmias

Statistical tests Ventricular arrhythmia results were analyzed using the Student s t test for paired data and assessed according to the difference between each individual s mean values before and after exercise testing as compared to zero Because of the possible non parametric

Ventricular arrhythmia 24 hours before and after maximal treadmill testing

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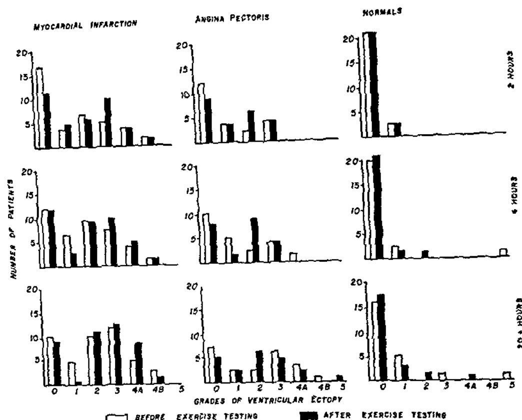


Fig 2 Distribution of maximal grades of ventricular ectopy in myocardial infarction angina pectoris, and normal patients for 2 4 and 20+ hour periods before and after exercise testing

testing as shown in Table II revealed no significant differences or discernible trend

Qualitative grade of ventricular ectopy The distribution of the maximal qualitative grades of ventricular ectopy detected for the same chronological two four and 20 plus hour periods before and after exercise testing during Holter recording examination in the three patient groups as shown in Fig 2 reveals no significant differences after exercise testing Although ventricular couplets (Grade 4A) in myocardial infarction patients and frequent unifocal (Grade 2) ventricular ectopic beats in angina pectoris were more prevalent *after* exercise testing there was no statistical difference Similarly the decrease in ventricular tachycardia (Grade 4B) in both myocardial infarction and angina pectoris patients after exercise testing could be interpreted as due to chance alone Evaluation of myocardial infarction patients with and without angina pectoris revealed an increase of frequent unifocal (Grade 2) ventricular ectopic beats in patients with angina and was similar to the increase noted in the patients who had angina pectoris alone Consistency of the presence of the various qualitative types of ventricular ectopy is indicated by the percentage of patients who displayed identical maximal qualitative grades when similar chronological two four and 20 plus hour periods were examined before and after exercise testing (Table III) Although more variability of maximal grade of ventricular ectopy in angina pectoris patients is apparent as compared to myocardial infarction

Table III Number of patients with unchanged *maximal* grades of ventricular ectopy during similar chronological 2 4 and 20 or more hour periods before and after exercise testing

	Total patients	Unchanged maximal grade VEB		
		2 hr	4 hr	20+ hr
Myocardial infarction	45	27 (60%)	26 (58%)	23 (51%)
Angina pectoris	22	10 (46)	9 (41%)	9 (41%)
Normal	23	21 (92%)	21 (91%)	17 (74%)

VEB = ventricular ectopic beats

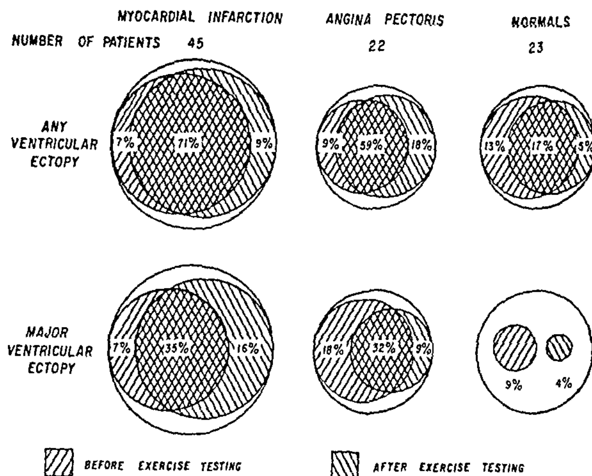


Fig 1 Percentage of myocardial infarction angina pectoris and normal patients with any or major ventricular ectopy as detected by 24 hour Holter recording before and after exercise testing

Table II Patients with any or major grades of ventricular ectopy detected during 24 hour Holter recordings before and after exercise testing

		Any VEB		*Major VEB*	
	Total patients	*Before exercise*	*After exercise*	*Before exercise*	*After exercise*
Myocardial infarction	45	35 (78%)	36 (80%)	19 (42%)	23 (51%)
Angina pectoris	22	15 (68%)	17 (77%)	11 (50%)	9 (41%)
Normal	23	7 (30%)	5 (22%)	2 (9%)	1 (4%)

VEB = ventricular ectopic beats

nature of ventricular ectopy, the Wilcoxon signed rank test was also utilized to analyze the data Significance was defined as a $p < 0.05$

Results

Detection of ventricular arrhythmia Fig 1 shows that ventricular arrhythmia was detected in all patient groups Major ventricular ectopy as defined by multifocal or multiform beats ventricular couplet, ventricular tachycardia or early cycle ventricular ectopic beats with R on T phenomenon, was notably small as expected in normal patients One normal patient demonstrated R on T phenomenon and another a multiform ventricular ectopic beat before exercise testing and one other normal patient displayed a ventricular couplet after exercise testing Consistency of ventricular arrhythmia in ischemic heart disease patients was evidenced by the majority of myocardial infarction and angina pectoris patients displaying ventricular ectopy on both Holter recording examinations (71 and 59 per cent respectively) Similarly those ischemic heart disease patients who displayed major ventricular ectopy tended to manifest it on both days (Fig 1) Comparison of the per cent of patients with any or major ventricular ectopy detected on Holter recordings performed before and after exercise

Discussion

The value of the ambulatory electrocardiographic Holter recording examination of patients in a variety of clinical disorders has become increasingly recognized in recent years.[8] Many patients with or suspected of cardiac disease in addition to a standard cardiological evaluation are often examined by exercise testing and long term Holter recording. In a practical sense since most patients present themselves for examination for a limited time period or the clinical disorder necessitates prompt diagnostic action, it is not unusual to perform exercise testing and to begin Holter recording examination at the same clinical visit or within the same 24 hour period. Because of this practical facet and the known arrhythmogenic effect of exercise testing in both normal subjects and in cardiac patients, it is of some concern and interest to determine if the occurrence of arrhythmia in the hours after exercise testing has been altered. Contemporary views often cite enhanced sympathetic nervous activity, increased catecholamine excretion,[8] regional myocardial ischemia[3] and tissue hypoxia and acidosis[4] as possible etiologic mechanisms of arrhythmia during exercise testing. It is reasonable to speculate that such factors may have some persistent effect on the occurrence of arrhythmia and not solely be limited to the short period of observation surrounding the time of an exercise test. This would thus be a factor to be considered when evaluating long term electrocardiographic data in addition to any inherent variability of arrhythmia which may occur in certain patient populations.

In the present investigation relatively active (New York Heart Association Class I II) ischemic heart disease patients and normal subjects revealed no statistically significant alteration of the occurrence of ventricular arrhythmia following maximal exercise treadmill testing. Comparison of ventricular ectopy measured in all patient groups for two, four and 20 or more hours after exercise testing with the ventricular ectopy of identical chronological periods of time prior to exercise testing was similar. This seemed to be generally true with regard to the occurrence of any ventricular ectopy, major ventricular ectopy, qualitative types of ventricular ectopy, and the quantitative frequency of ventricular ectopy in all patient groups. Angina pectoris patients curiously displayed less complex qualitative types of ventricular ectopy at lower frequencies following exercise testing especially in the initial hours following exercise but this did not achieve statistical significance. Such observations may have been related to the sample population studied. Similar observations of the prolonged effects of exercise testing on ventricular ectopy as examined in this study have not been reported to the authors' knowledge and are unavailable for comparison. Nevertheless, these findings do support the observed history of safety of maximal exercise testing as attested to by the paucity of morbidity or mortality that might be attributed to arrhythmia in the post exercise period.

Other observations during this study are similar to previously reported studies of ventricular ectopy in ischemic heart disease patients and normal subjects. The prevalence of any ventricular ectopy in approximately 80 per cent and major ventricular ectopy in approximately 50 per cent of ischemic heart disease patients as detected by 24 hour Holter recording is similar to other studies.[9] Similarly, the estimated prevalence of ventricular ectopy in approximately 30 per cent of normal subjects was found in this study despite the relative paucity and non homogeneity of such reported Holter recording data in normal populations. The lack of association between qualitative types and frequency of ventricular ectopy as detected by long term Holter recording and exercise test parameters has been previously observed.[9] Although observations of ventricular ectopy during exercise testing have identified an association between exercise heart rate, abnormal wall motion, severity of coronary artery disease and frequency and type of ventricular ectopy, such correlates with regard to ventricular arrhythmia detected by Holter recording are unknown.

These observations add additional data to the increasing knowledge of cardiac dysrhythmia in both ischemic heart disease and normal subjects as detected by long term ambulatory electrocardiographic Holter recordings.

Summary

To determine if maximal exercise treadmill testing influences the occurence of ventricular arrhythmia in the hours after exercise, 45 myocardial infarction and 22 angina pectoris patients (New York Heart Association Class I II) and 23 normal subjects were examined with 24 hour ambulatory electrocardiographic Holter recordings before and after exercise testing

Table IV Frequency of ventricular ectopic beats per hour for the same chronological 2 4 and 20+ hour periods before and after exercise testing

	Patients	Mean frequency of VEB/hr ± SEM		Mean difference ± SED	P value
		Before ETT	After ETT		
Myocardial infarction					
2 hours	35	59 33 ± 26 72	51 98 ± 27 87	7 34 ± 18 67	
4 hours	35	58 08 ± 25 58	51 36 ± 27 33	6 72 ± 15 38	
20+ hours	32	38 02 ± 16 68	35 70 ± 16 06	2 32 ± 7 38	
Angina pectoris					
2 hours	21	10 12 ± 5 31	3 58 ± 0 93	6 53 ± 4 97	
4 hours	21	10 41 ± 5 72	3 06 ± 0 71	7 35 ± 5 61	
20+ hours	20	6 83 ± 3 53	3 43 ± 1 06	3 40 ± 3 00	
Normal					
2 hours	23	0 04 ± 0 04	0 09 ± 0 06	0 04 ± 0 04	*
4 hours	23	0 09 ± 0 08	0 10 ± 0 09	0 02 ± 0 01	
20+ hours	23	0 07 ± 0 08	0 04 ± 0 02	0 02 ± 0 03	

Abbreviations VEB/hr ventricular ectopic beats per hour SEM = standard error of the mean SED = standard error of the difference
* = not statistically significant

Table V Mean parameters found during exercise treadmill testing in each study group

	Patients	Minutes exercise ± SD	FAI ± SD	Maximum heart rate (beats/min)	Maximum Sys BP (mm Hg)	Maximal PR
Myocardial infarction	45	7 5 ± 6 6	17 ± 21	142 ± 18	164 ± 24	234 ± 49
Angina pectoris	22	6 5 ± 2 0	16 ± 14	149 ± 18	183 ± 31	263 ± 65
Normal	23	10 0 ± 2 2	−4 ± 16	172 ± 13	197 ± 24	342 ± 43

Abbreviations SD = standard deviation FAI = functional aerobic impairment BP = blood pressure PR = systolic pressure × heart rate

patients for all chronological periods examined, the alteration of qualitative grade in angina pectoris patients is skewed toward lower grades of ventricular ectopy (Fig 2) especially in the immediate hours after exercise

Quantitative frequency of ventricular ectopy Only those patients who had complete hourly data from the entire chronological period being examined were included in the evaluation of ventricular ectopic beat frequency Patients with more than 20 hours of Holter recording data had all available hours included in the determination of their mean frequency of ventricular ectopy per hour Table IV shows that no statistically significant difference existed in the mean frequency of ventricular ectopic beats per hour in any patient group when compared for the same chronological two, four and 20 plus hour period before and after exercise treadmill testing Noteworthy is the definite higher mean frequency of ventricular ectopy in patients who have sustained myocardial infarction as compared to angina pectoris and normal patients and the tendency for angina pectoris patients to decrease their mean frequency of ventricular ectopy after exercise (not statistically significant)

Parameters measured during exercise testing Table V shows that the mean duration of exercise maximum heart rate maximum systolic blood pressure, and pressure-rate product were substantially greater in normal patients with less functional aerobic impairment than in myocardial infarction and angina pectoris patients There was no discernible relationship detected between any of the measured variables and the likelihood to increase or decrease quantitative frequency or qualitative grades of ventricular ectopy after exercise testing Similarly none of the measured variables of exercise emerged as an indicator of which patients were likely to show the same qualitative grades of ventricular ectopy consistently before and after exercise testing Examination of the persons in each patient group who manifested greater than 20 per cent variation of frequency of ventricular ectopy during the chronological periods evaluated before and after exercise testing disclosed no correlation to any of the measured exercise variables

Heparin neutralizing activity and coronary artery disease

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In 1948 Conley and co workers reported that patients with thrombocytopenia had an increased sensitivity to heparin and suggested that platelets could counteract the anticoagulant effects of heparin This observation was subsequently confirmed by other workers who demonstrated that platelets contain material capable of neutralizing heparin and referred to it as platelet factor 4 (PF) In 1968 Niewiarowski and colleagues[3] reported that purified PF prepared from platelet homogenates induced paracoagulation (nonenzymatic precipitation of soluble fibrin monomer complexes) and that it enhanced adenosine diphosphate (ADP) induced platelet aggregation It seems possible that this proteinaceous material could have included a histone like protein similar to that precipitated from an acid extract of a platelet lysate by Kopéc and associates[5] as both preparations [6] neutralized heparin induced paracoagulation and were derived from disrupted platelets Subsequently Nath and co workers reported that a heparin neutralizing protein released from platelets by collagen did not enhance polymerization of fibrin A low molecular weight basic protein bound to a proteoglycan carrier and released from platelets by thrombin was also found to be capable of neutralizing heparin but not of inducing paracoagulation Although it is not known whether the platelet protein(s) capable of inducing paracoagulation [4] are released during aggregation it has been suggested[4] that soluble fibrin monomer complexes paracoagulated by PF, may be involved in attachment of platelets to each other

Platelets are generally believed to play an important role in the initiation of arterial thrombosis Previous work from this laboratory has shown that slow platelet disaggregation (less than 10 per cent disaggregation at 3 minutes after peak 1 7 μM ADP induced aggregation) occurs much more frequently in the platelet rich plasma (PRP) of men with occlusive arterial diseases than in control men We suspected that the release of heparin neutralizing activity (HNA) might be one of the factors which controls the rate of platelet disaggregation and in this study have determined whether platelets which disaggregate slowly release more HNA during ADP induced aggregation than platelets which disaggregate more rapidly

Subjects

Twenty one men with a myocardial infarct documented by electrocardiogram and 11 men without a history of a myocardial infarct or of angina pectoris were selected on the basis of having taken no aspirin other anti inflammatory agents or anticoagulants within the preceding 2 weeks and of having no history of excessive bleeding liver disease renal disease thrombophlebitis recent surgery or recent angiography Only one man had a myocardial infarct less than 2 months before HNA was assayed None of the men had severe arterial disease of the extremities but four of the men with myocardial infarcts also

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Comparison of qualitative and quantitative ventricular arrhythmia detected during identical chronological two-, four-, and 20- or more hour periods before and after exercise testing in each patient revealed no statistically significant difference in any patient group. The prevalence of ventricular ectopy in 80 per cent of ischemic heart disease patients and 30 per cent of normal subjects as detected by 24 hour Holter recordings was similar to previous studies.

It is concluded that in ambulatory ischemic heart disease patients (New York Heart Association Class I-II) and normal subjects maximal treadmill testing does not significantly affect the occurrence of ventricular arrhythmia in the hours after exercise.

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Table I HNA* Release during 1 7 µM ADP induced platelet aggregation in PRP of 21 men with and 11 men without coronary artery disease

	Type I disaggregation		Type II disaggregation		Type III disaggregation		Type IV disaggregation	
	No of men	*No of men with HNA release > 5%*	*No of men*	*No of men with HNA release > 5%*	*No of men*	*No of men with HNA release > 5%*	*No of men*	*No of men with HNA release > 5%*
CAD	8	0	6	0	[illegible]	1 ([illegible]9% released)	5	5 (34 51% released)
No CAD	3	0	4	1 (8% released)	4	1 ([illegible]1% released)	0	0

HNA Heparin n t alizi g act vity ADP adenos e d phosphate PRP plat let rich plasma CAD coronary rtery disease

Table II Comparisons of platelet variables of 21 men with and 11 men without coronary artery disease (mean ± S D)

	Platelet count (×10 /µl)	*Aggregation (chart units)*	*HNA in untreated PRP (milliunits/ml)*	*Total platelet HNA (milliunits/ml)*	*HNA/platelet (nanounits)*	*% of HNA relea ed by ADP*
CAD	318 ± 128	38 ± 19	168 ± 26	4[illegible]4 ± 116	1 43 ± 0 40	13 ± 19
No CAD	[illegible] 9 ± 78	31 ± 10	139 ± 22	387 ± 9[illegible]	1 4[illegible] ± 0 30	3 ± 6
Probability†	> 0 1	> 0 1	< 0 01	> 0 1	> 0 1	> 0 0

HNA in PRP treated w th Triton X 100 minus HNA i PRP treated with 0 9% NaCl
†Det rm ned by the W l xon rank sum test

Table III Comparisons of disaggregation Type IV with Types I II and III (mean ± S D)

T pe (no tested)	*Platelet count (×10 /µl)*	*Aggregation (chart units)*	*HNA in untreated PRP (milliunits/ml)*	*Total platelet HNA (milliunits/ml)*	*HNA/platelet (nanounits)*	*% of HNA released by ADP*
Type IV (5)	456 + 104	63 ± 11	19[illegible] ± 16	501 ± 41	1 16 ± 0 34	43 ± 7
Types I II and III (27)	276 + 92	30 ± 11	151 ± [illegible]	395 ± 109	1 48 ± 0 35	3 ± 7
Probability†	< 0 01	< 0 01	< 0 01	< 0 05	> 0 05	< 0 01

HNA in PRP tr ated w th Trit n X 100 minus HNA in PRP treated with 0 9% NaCl
†Det rmined by th W lc on ank sum test.

that of the first phase in only three PRP In contrast all five of the Type IV PRP had at least 34 per cent HNA release and either a prominent second phase of aggregation of fusion of the first and second phases

Table II shows comparisons of several platelet variables of men with and without coronary artery disease The only difference significant at the 5 per cent level was the greater HNA in untreated PRP of patients with coronary artery disease In *Table III* a comparison of the same variables was made between Type IV PRP and the PRP of disaggregation Types I II and III combined Each of the variables except the HNA per platelet was significantly greater with Type IV PRP

For the 32 men (21 with and 11 without coronary artery disease) the correlation coefficient between the platelet count in PRP and HNA in untreated PRP was 0 62 (P < 0 001) and that between platelet count and platelet aggregation was 0 27 (P > 0 1)

The serum cholesterol concentration of the five men with Type IV disaggregation ranged from 165 to 250 mg /100 ml

Discussion

This investigation confirms our previous report[9] that the disaggregation of 1 7 µM ADP induced platelet aggregates occurs at a very slow rate (Type IV) more frequently in the PRP of men with coronary artery disease (Table I) The

had a cerebrovascular accident 2 months to 5 years prior to the assay of HNA

The mean age of the men with a myocardial infarct was 57 6 years with a range of 39 to 79 years The mean age of the men without a myocardial infarct was 50 0 years with a range of 34 to 63 years The mean ages of the two groups were not significantly different (P > 0 05 by the Wilcoxon rank sum test)

Methods

PRP was prepared as previously described[9] and left at room temperature for 55 minutes before aggregation procedures were begun Platelet counts of PRP were done in duplicate using phase-contrast microscopy

Platelet aggregation was induced in PRP by a modification[9] of the method of Born and Cross[10] The span of the recorder (Bausch and Lomb VOM 5) was set at 10 chart units for PRP and 90 chart units for platelet poor plasma (PPP) PRP was incubated at 37° C for 5 minutes before it was stirred in a platelet aggregometer (Chrono Log Corp) at 1800 rpm After stirring 0 4 ml of PRP for approximately 1 minute 0 04 ml of ADP (Sigma Chemical Co) in 0 9 per cent NaCl was added to induce aggregation with a final ADP concentration of 1 7 μM

Disaggregation measured as the decrement of light transmission found 3 minutes after maximum light transmission occurred was expressed as a percentage of the maximum increment observed after the addition of ADP and classified[9] as Type I (50 per cent or more) Type II (30 to 49 per cent) Type III (10 to 29 per cent) or Type IV (< 10 per cent) We believe that the most meaningful way to express disaggregation is as a function of aggregation since the maximum disaggregation which can occur is 100 per cent of the preceding aggregation

HNA was determined with a method described by Harada and Zucker[11] which consists of determining the heparin thrombin time (HTT) with serial heparin dilutions After incubation of 0 2 ml of PRP at 37° C for 3 minutes in a plastic cuvette in a Coagulatron Model L/S 1 (I nter Scientific, Inc) a stir bar and 0 04 ml of heparin (Upjohn Company) in 0 9 per cent NaCl (heparin concentrations ranging from 0 2 to 5 5 units/ml) was added Immediately 0 1 ml of thrombin (Parke, Davis & Company), 10 units/ml in 0 9 per cent NaCl was added using an automatic pipette which started the timer Three to eight determinations of HTT were done to obtain the mean value for each concentration of heparin giving an HTT immediately above and below 20 seconds The concentration of heparin giving an HTT of 20 seconds was determined graphically and expressed in milliunits per ml of PRP to give HNA as described by Donati and colleagues[12]

To release all HNA from platelets, one volume of PRP was mixed with 0 025 volume of 20 per cent Triton X 100, as described by Niewiarowski and associates,[13] and the HTT was determined The procedure was repeated using 0 9 per cent NaCl instead of the 20 per cent Triton X 100 to obtain the HNA of PRP The values obtained in these PRP were multiplied by 102 5 per cent to correct for the dilution of PRP by Triton X 100 or 0 9 per cent NaCl The difference between these two values was taken as total HNA present in the platelets, and the HNA per platelet was obtained by dividing total HNA by the platelet count and was expressed as nanounits of heparin neutralized per platelet To determine the HNA released during 1 7 μM ADP induced aggregation, PRP after stirring with ADP or 0 9 per cent NaCl was used to determine the HTT The duration of stirring PRP was the same with 0 9 per cent NaCl as with ADP (approximately 3 minutes after peak aggregation occurred) The HNA values obtained were multiplied by 110 per cent to correct for dilution of PRP with ADP or 0 9 per cent NaCl The difference between the two is the HNA released during aggregation with ADP The fraction of total HNA released by ADP was obtained by dividing that released by ADP by that released by Triton X 100 Negative values for HNA release were obtained frequently and the lowest one was −5 per cent We therefore considered ± 5 per cent HNA release by ADP as nonrelease

For convenience PRP treated with 0 9 per cent NaCl is hereafter usually referred to as untreated PRP

Results

Table I shows that only three of the 27 men with Type I II or III disaggregation had more than 5 per cent release of HNA during ADP induced platelet aggregation The platelets of one of these men disaggregated only 11 per cent and released 29 per cent of their HNA Of the 27 PRP, 21 had a second phase although the light transmission at the peak of the second phase exceeded

in which disaggregation was more rapid (Tables I and III) suggested that release of HNA may contribute to enhanced platelet aggregation and slow disaggregation possibly through precipitation of soluble fibrin monomer complexes on the platelet surface membranes as previously postulated However the heparin neutralizing protein isolated after its release from platelets by thrombin does not precipitate soluble fibrin monomer complexes[4] Walsh has discussed the possibility that circulating human blood may contain the minute quantities of heparin necessary to potentiate the inactivation of factor Xa by antifactor Xa and that inactivation of factor Xa on the platelet surface may be prevented by the release of HNA The prevention of inactivation of factor Xa on the platelet surface by HNA would tend to promote the generation of thrombin on which irreversible ADP induced platelet aggregation appears to depend

Although PF has been reported to be released early in the course of the release reaction in parallel with ADP[3] and serotonin which are known to be stored in dense granules our experiments showed that large amounts of HNA were released only when aggregation was relatively irreversible and that a reversible second phase was often associated with no detectable release of HNA The most striking example seen in our laboratory of a reversible second phase with no detectable release of HNA is shown in Fig 1 This dissociation of HNA release from the second phase of aggregation might be indirect evidence to support the hypothesis that HNA is not stored in the same granules which contain ADP and serotonin This concept was offered by Weiss and Rogers who found a normal total amount of PF activity in the platelets of patients with storage pool disease and by Walsh and Gagnatelli[2] who also reported normal HNA activity in the platelets of four of six patients with storage pool disease Their platelets contain fewer dense granules than normal platelets and are n at least three of the constituents of age granules (ADP ATP and seroto ther piece of evidence consistent with torage sites for HNA is the observation ho and colleagues[2] who found increased f nucleotides but not of PF from of patients with Type II hyperlipopro

Recently Broekman and associates[7-9] an ultracentrifugal fractionation of in which the highest concentrations of HNA and serotonin appeared in different fractions

The potential significance of Type IV disaggregation is that the rate of platelet disaggregation could play a role in determining whether or not thrombosis supervenes when platelets contact exposed subendothelial connective tissue We have speculated that individuals whose platelets may be capable of rapid disaggregation following aggregation in response to a fissure of an atherosclerotic plaque or exposed connective tissue may be protected from the formation of an occluding thrombus and that those whose platelets disaggregate slowly may be more likely to respond with the development of thrombosis

Summary

It has been previously shown and confirmed in the present investigation that the disaggregation of adenosine diphosphate (ADP) induced platelet aggregates occurs at a slow rate more frequently in the platelet rich plasma (PRP) of men with coronary artery disease ADP induced platelet aggregation was studied in the citrated PRP of 32 men (21 with and 11 without coronary artery disease) to determine the relation between release of heparin *neutralizing activity (HNA)* from platelets *and the rate of* platelet disaggregation Each of the five PRP with slow (less than 10 per *cent)* disaggregation were from men with coronary artery disease Platelets from these five PRP released from 34 to 51 per cent of their content of HNA during ADP induced aggregation in contrast to the 27 PRP with more rapid disaggregation only three of which had a detectable release of HNA Of the latter 27 PRP 21 had a second phase of aggregation which usually reached a peak of light transmission less than that of the first phase These data are consistent with (but do not prove) the hypothesis that HNA released during aggregation may be one of the factors tending to prevent disaggregation of ADP induced platelet aggregates

The authors gratefully acknowledge the secretarial assistance of Mrs Mary D Vance

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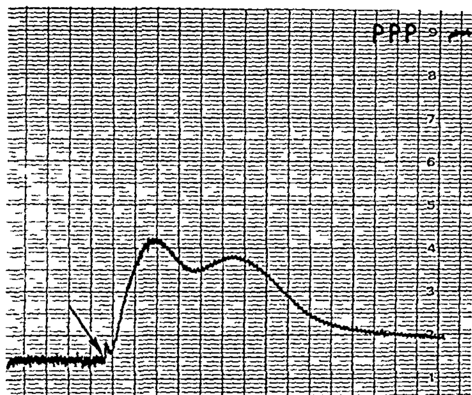


Fig 1 Light transmission record of stirred platelet rich plasma before and after addition of adenosine diphosphate (arrow) and of platelet poor plasma (PPP) Space between vertical lines represents 15 sec The record indicates biphasic aggregation followed by greater than 50 per cent disaggregation 3 minutes after maximal aggregation (Type I) No release of heparin neutralizing activity was found at completion of this tracing

present study shows that a much greater proportion of the HNA of the platelets of Type IV PRP is released during aggregation than is released by the platelets of men with more rapid disaggregation In addition, increased HNA is found in untreated Type IV PRP (Table III)

The HNA in untreated PRP may be derived from platelets in vitro due to procedures used in preparing plasma and/or in vivo due to platelet destruction which has been shown to be increased in patients with atherosclerosis[14] or arterial thromboembolism[15] The correlation coefficient (0 62, $P < 0\,001$) between the platelet count and HNA in untreated PRP is consistent with a platelet origin of some of the HNA in PRP Plasma HNA may also come from substances[6, 16, 17] not derived from platelets We consider HNA in plasma to probably originate from multiple sources and subtract the value of saline treated PRP from the value found after adding Triton X 100 or ADP to PRP to obtain the total HNA present in the platelets or the amount of HNA released by ADP respectively

The elevated HNA in the untreated PRP of men with coronary artery disease (Table II) is consistent with the observations of O Brien and associates[18] who reported elevated PF_4 levels in both PRP and PPP of men with coronary artery disease Also Cotton and co workers[19] reported an elevation of plasma HNA in patients with occlusive peripheral vascular disease compared with apparently healthy controls of the same age Apparently healthy elderly subjects had elevated HNA in PPP when compared with younger subjects and elderly subjects with occlusive arterial diseases had significantly higher values than elderly healthy subjects[20] Atherosclerotic plaques would seem an ideal site for platelet damage to release HNA and may explain the higher levels of plasma HNA in patients with coronary artery disease and peripheral vascular disease

The platelets in Type IV PRP aggregated irreversibly with a relatively low concentration of ADP (1 7 μM) The reason for the lower threshold of irreversible aggregation of these platelets is not clear The serum cholesterol levels of the five men with Type IV disaggregation were within normal limits Therefore we do not think that Type II hyperlipoproteinemia was responsible for their increased platelet sensitivity to ADP[1] PF_4 does not aggregate platelets in human citrated PRP, but it potentiates the aggregating action of ADP[5] The observation that Type IV platelet disaggregation was associated with a large release of HNA while little or no release of HNA occurred in PRP

in which disaggregation was more rapid (Tables I and III) suggested that release of HNA may contribute to enhanced platelet aggregation and slow disaggregation possibly through precipitation of soluble fibrin monomer complexes on the platelet surface membranes as previously postulated[5] However the heparin neutralizing protein isolated after its release from platelets by thrombin does not precipitate soluble fibrin monomer complexes[8] Walsh has discussed the possibility that circulating human blood may contain the minute quantities of heparin necessary to potentiate the inactivation of factor Xa by antifactor Xa and that inactivation of factor Xa on the platelet surface may be prevented by the release of HNA The prevention of inactivation of factor Xa on the platelet surface by HNA would tend to promote the generation of thrombin on which irreversible ADP induced platelet aggregation appears to depend [3]

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The potential significance of Type IV disaggregation is that the rate of platelet disaggregation could play a role in determining whether or not thrombosis supervenes when platelets contact exposed subendothelial connective tissue We have speculated that individuals whose platelets may be capable of rapid disaggregation following aggregation in response to a fissure of an atherosclerotic plaque or exposed connective tissue may be protected from the formation of an occluding thrombus and that those whose platelets disaggregate slowly may be more likely to respond with the development of thrombosis

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Effect of stimulation of somatic nerves on the ventricular fibrillation threshold in dogs

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Changes in activity of autonomic nerves to the heart have been implicated in the genesis of cardiac arrhythmias for many years Recently Lown and Verrier have reviewed the literature concerning the possible influence of the sympathetic nervous system in sudden death due to ventricular fibrillation and have suggested that changes in cardiac neural activity may be a *transient risk factor* in this situation One aspect of the role of the sympathetic nervous system that has not received much attention is the influence of somatosympathetic reflexes upon the development of cardiac arrhythmias Can activation of somatic afferent fibers (e g pain) induce changes in cardiac sympathetic nerve activity which will either facilitate or inhibit the development of arrhythmias under certain conditions?

Observations on the circulatory effects of stimulation of peripheral nerves have appeared in the literature for over 100 years (for review see Johansson) but there is little information concerning the cardiac effects of these reflexes While detailed electrophysiological studies have increased the knowledge on the central connections and electrophysiological mechanisms of somatosympathetic reflexes there is still much work needed to determine the general involvement of these reflexes in normal physiological and pathological conditions Too frequently effector organ responses have been only descriptive and afferent fibers involved were not actually determined In addition many of the responses that have been described were obtained in experiments in which other reflexes had been attenuated thus tending to eliminate possible interactions between somatosympathetic reflexes and other autonomic reflexes

The purpose of this study was to investigate the effect of activation of somatosympathetic reflexes on the vulnerability of the ventricles to fibrillation to determine the afferent fiber groups involved in the response and to attempt to investigate the mechanisms responsible for the observed changes The vulnerability of the ventricles to fibrillation was assessed by determining ventricular fibrillation threshold (VFT) The amount of current required to induce ventricular fibrillation is decreased by those conditions which promote development of cardiac arrhythmias and increased by those which tend to make the myocardium less vulnerable An increase in cardiac sympathetic activity results in a decrease in VFT while stellectomy beta adrenergic blockade and reflex inhibition of sympathetic activity result in an increase in VFT

Methods

Experiments were done on male mongrel dogs (15 to 20 kilograms) initially anesthetized with an intravenous injection of α chloralose (75 mg /Kg) and urethane (500 mg /Kg) A stable level of anesthesia was maintained by an intravenous infusion of α chloralose and urethane (20 to 40 mg /Kg hr each) using an infusion pump (Harvard Apparatus Co) Dogs were intubated and ventilated (Harvard pump) with air at a rate and depth of ventilation to maintain the end tidal CO concentration at approximately 5 per cent (Beckman LB 1 gas analyzer) Rectal temperature was maintained at 38 ± 1° C by a heating

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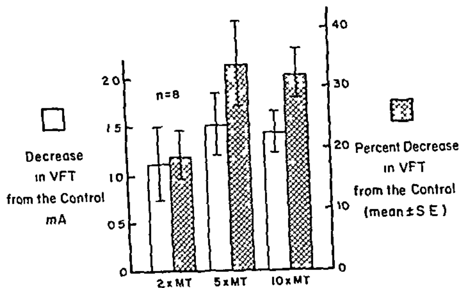


Fig. 2. Change in VFT during stimulation of the median nerve (4 Hz, 2 msec. duration) at various multiples of motor threshold *(MT)*. All of the changes were significant when compared to the corresponding controls. Using the t test for dependent samples the 5 and 10 × MT responses were significantly ($P < 0.05$) greater than the 2 × MT response.

400 Hz and at intensities ranging from 2 to 10 times the motor threshold (MT). In the case of the cutaneous nerve (sural), the stimulus intensity was expressed as a multiple of the response threshold (RT) which was defined as the minimal voltage which produced a measurable blood pressure response. The order of nerve stimulation was randomized among animals and a control VFT was determined prior to each experimental condition. In several experiments the change in VFT during stimulation of somatic nerves was compared before and after β adrenergic blockade with dl propranolol (1 mg./Kg., intravenously). The types of afferent fibers activated by the various intensities of nerve stimulation were identified by recording the compound action potentials on a storage oscilloscope (Tektronix type 564). The nerves were stimulated using the same stimulation parameters as in the VFT experiments and conduction velocities were calculated using the differences in latency and conduction distance between two stimulation sites and a common recording site. The fiber types activated were identified by their conduction velocities. Group I fibers were identified as those conducting at 72 to 120 M./sec., Group II at 24 to 72 M./sec., Group III at 6 to 24 M./sec., and Group IV at 0.5 to 2 M./sec.

Changes in VFT during nerve stimulations were expressed as means ± standard error (S.E.). The percent change in VFT with respect to control values was also calculated. The t test for dependent samples was used in instances when only one or two pairs of means were to be compared. For comparisons of more than two pairs of means, Duncan's New Multiple Range Test was used. With this test it was possible to determine whether there was a significant difference between control experimental VFT's or between the various experimental VFT's. In one series heterogeneity of variance precluded the use of Duncan's test; these data were subjected to non-parametric analyses using the Wilcoxon Signed Rank Test. The probability of $P < 0.05$ was accepted as the minimal level which indicated a statistically significant difference.

Results

Control experiments. To investigate whether the determination of VFT would change with time during an experiment, VFT was determined every 30 minutes over a 3 hour period. The mean value (±S.E.) for VFT over a 3 hour period was found to be 2.8 ± 0.1 mA. VFT's (±S.E.) calculated for each time interval are shown in Fig. 1. There was no significant change in VFT over the 3 hour period.

The effect on VFT of stimulating somatic nerves. In eight dogs the median nerve was stimulated at 4 Hz, 2 msec. duration and at intensities of 2, 5, and 10 × MT. Absolute changes and per cent changes between VFT's

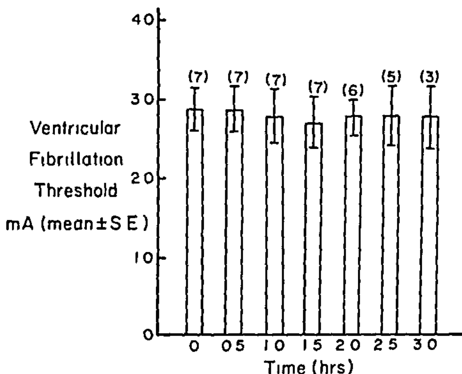


Fig 1 Effect of successive VFT determinations on the VFT *Numbers in parentheses* represent the number of animals at the time indicated There was no significant difference between the means during the experimental period

pad controlled by a temperature controller (Yellow Springs Instrument Co)

Arterial blood pressure was measured from a cannulated femoral artery connected to a pressure transducer (Statham P23 AC) The ECG was amplified (Grass 7P1) and displayed on an oscilloscope Heart rate was obtained by using the arterial pressure or ECG signal to trigger a tachograph (7P4) All variables were recorded on a Grass Model 7 polygraph

The right side of the chest was opened along the fifth intercostal space and the pericardium was opened and sutured to the chest wall to form a pericardial cradle for the heart The sinoatrial node was crushed and an acrylic plaque in which double bipolar silver electrodes were embedded was sutured onto the surface of the right ventricle The interelectrode distance was approximately 10 mm and the d c resistance of the electrodes in saline was less than 2 kilohms

VFT was determined by using essentially the technique described by Kniffen and associates[12] A train of pulses of known intensity was delivered to the ventricles during the vulnerable period of ventricular systole, and the minimal current which induced ventricular fibrillation was defined as the VFT The ventricles were paced by 2 msec electrical pulses at 3 Hz from a Grass SD5 stimulator at twice threshold intensity through one set of electrodes A 310 msec train of fibrillatory pulses (60 Hz, 2 msec duration) delivered by a Grass (S48) stimulator was synchronized to the pacing stimulator and triggered by an electronic counting device after every tenth pacing stimulus Three trains of pulses at a given intensity were tested before increasing the current to the next level The peak current intensity was preset on a constant current unit (Grass CCU 1) and the intensity was increased in increments of 0 5 mA until ventricular fibrillation occurred Ventricular fibrillation was immediately terminated using a Burdick d c defibrillator with a 50 watt second discharge delivered to the exposed heart Thirty minutes were allowed between determinations to allow complete stabilization of cardiovascular parameters

The effect of stimulation of somatic nerves on the VFT was studied by stimulating mixed nerves in the forelimb and hindlimb as well as by stimulating cutaneous and muscle nerves in the hindlimb The nerves were isolated bipolar platinum alloy sleeve electrodes were attached to the nerve trunks and the nerves were packed in gauze pads soaked in mineral oil to prevent nerve desiccation and current spread The nerves were stimulated through a stimulus isolation unit (Grass SIU5) with 2 msec rectangular pulses from a Grass S4 stimulator at frequencies of 4 or

Table I Afferent nerve fibers activated by stimulation of somatic nerves used during VFT determinations

Stimulation intensity	*Fiber groups activated (range of conduction velocities M/sec)*
Median nerve (n = 3)	
2 MT	I (90-100) II (30-68)
5 MT	I II III (8-70)
0 MT	I II III IV (o)
Tibial nerve (n 3)	
2 MT	I (83 150) II (4 63)
5 MT	I II III (18 20)
Obturator nerve (n = 3)	
2 MT	I (100-120) II (55 60)
5 MT	I II III (0 25)
Sural nerve (n = 1)	
5 or 10 RT†	II (40) III (14) IV (1 5)

MT = Motor threshold
RT = Response threshold (see text for definition)

The changes in VFT between values determined during nerve stimulation and the corresponding control determinations are shown in Fig 3 Stimulation of the median or tibial nerve at 5 × MT 4 Hz significantly ($P < 0.05$) lowered the VFT Stimulation at 5 × MT 400 Hz produced changes in VFT which were statistically significant ($P < 0.05$) using non parametric statistics (Wilcoxon Signed Rank Test) This type of statistical analysis was used since heterogeneity of variance precluded the use of Duncan s Test There was no significant difference between the changes in VFT produced by the various nerve stimulations

The effect of stimulating muscle or cutaneous afferent fibers was studied by stimulating the left obturator nerve and the caudal cutaneous sural nerve Changes between VFT values during nerve stimulation and the corresponding controls are shown in Fig 4 When compared to the control VFT the VFT was decreased significantly by stimulation of the obturator or sural nerve There was no significant difference between the changes in VFT produced by nerve stimulation nor was there any difference between any of the control VFTs

In five dogs the change in VFT during stimulation of the median nerve (5 × MT 2 msec 4 Hz) was determined before and after administration of propranolol (1 0 mg /Kg intravenously) Before propranolol stimulation of the median nerve significantly ($P < 0.01$) decreased VFT after propranolol VFT during stimulation of the median nerve was not significantly different from the control The blood pressure response to stimulation of the median nerve was similar in both conditions

Arterial blood pressure responses Stimulation of somatic nerves produced transient changes in arterial blood pressure which except in the high intensity and high frequency stimulations usually had returned toward control before VFT was determined Peak pressor responses ranged from 15 to 90 mm Hg for the 5 × MT stimulations of the median tibial and obturator nerves at 4 or 400 Hz Stimulation of the median and tibial nerves at 2 × MT and the sural nerve at 5 or 10 × RT produced no significant change in mean arterial pressure

Compound action potentials To determine which afferent fibers were being activated in these experiments the compound action potentials produced by these nerve stimulations were analyzed in four dogs The range of recorded conduction velocities for the wave components, and the corresponding fiber groups activated by the nerve stimulations are shown in Table I Stimulations of the median tibial and obturator nerves at 5 × MT activated afferent fibers of Groups I II and III In the median and tibial nerves Groups I and II were activated by 2 × MT stimulations In the median nerve Group IV fibers were also activated by stimulation at 10 × MT Sural nerve action potentials were recorded in only one dog Fibers of Groups II to IV were found to be activated by stimulation at either 5 or 10 × RT

Discussion

The technique of determining VFT appears to provide an index of the vulnerability of the heart to the development of arrhythmias Various investigators have shown that increased sympathetic nervous system activity produces a decrease in VFT [1] In the present study various somatic nerves were stimulated to determine whether somatosympathetic reflexes could influence the VFT

In the first series of experiments it was found that the VFT remained constant for up to three hours when control VFT determinations were

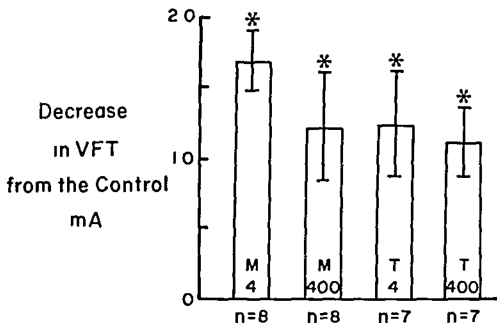


Fig 3 Change in VFT during stimulation (2 msec duration 5 × MT) of the median *(M)* and tibial *(T)* nerves at 4 or 400 Hz * $P < 0.05$

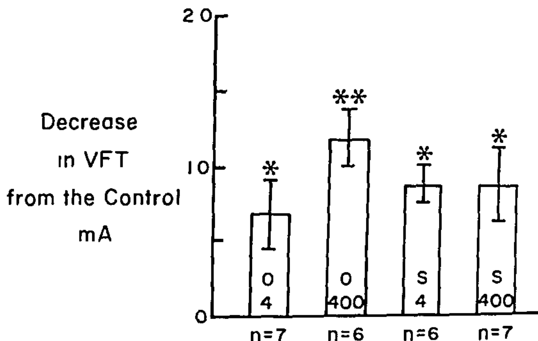


Fig 4 Change in VFT during stimulation (2 msec duration 5 × MT) of the obturator *(O)* and sural *(S)* nerves at 4 or 400 Hz * $P < 0.05$ ** $P < 0.01$

determined during stimulation of the median nerve and the corresponding control VFT s are shown in Fig 2 There was no significant difference between any of the control values Stimulation of the median nerve at all intensities produced significant decreases in the VFT Using the t test for dependent variables the decreases in VFT during 5 × MT and 10 × MT stimulations were shown to be significantly ($P < 0.05$) greater than those during 2 × MT stimulations

In six of the same animals stimulation of the tibial nerve at 4 Hz 2 msec duration and 2 × MT produced a significant ($P < 0.05$) decrease in VFT The change was similar to those resulting from stimulation of the median nerve at the same parameters i e a mean decrease (±S E) of 1 1 ± 0 4 mA corresponding to a 21 per cent change in the VFT

To investigate the effect of different frequencies of stimulation either the right tibial or the contralateral median nerve was stimulated at 5 × MT 2 msec duration and at 4 Hz or 400 Hz

only small additional increases in the response This does not rule out the possibility that the changes in sympathetic activity produced by stimulation of Group II and III were maximal changes and no further increase was possible Alternatively a 40 to 50 per cent decrease in VFT may be the maximum possible change in VFT produced by altered sympathetic tone Kliks and co-workers reported a 42 per cent decrease in VFT in response to maximal stimulation of the stellate ganglion and Kolman and associates reported a 49 per cent decrease under similar conditions

Group IV afferent fibers subserve pain receptors metabolic receptors in muscle and certain mechanoreceptors in the joints Pain passive limb movements and muscle contraction are all strong stimuli for reflex cardiovascular responses Therefore Group IV afferent stimulation alone would probably produce changes in sympathetic activity but may not increase the magnitude of the response when superimposed on stimulation of Groups II and III

Sato and Schmidt reported that stimulation of afferents from cutaneous and muscle areas resulted in different changes in sympathetic nerve activity although Johansson produced similar changes in arterial blood pressure when stimulating muscle or cutaneous nerves In the present study stimulation of the sural or obturator nerves produced changes in the VFT which were not significantly different from one another however the changes in VFT may have been maximal at the stimulus intensity used in this series

Somatosympathetic reflexes consist of several components which are organized at different levels of the central nervous system The spinal component produces changes in sympathetic efferent activity which are maximal in magnitude at the segmental level of afferent input Although the median nerve enters the spinal cord segmentally much closer to the heart than does the tibial nerve no difference was seen in the magnitude of the VFT changes in response to 5 × MT stimulation Similarly when 2 × MT stimulations of these nerves were used to compare submaximal VFT responses, no difference between the decreases in VFT was seen These findings suggest in agreement with Koizumi and Brooks that the spinal component is normally inhibited in an animal with the central nervous system intact and that the major contribution to the sympathetic responses evoked in these experiments was from the supraspinal excitatory components of somatosympathetic reflexes This would explain the fact that there were no differences between the responses to median and tibial nerve stimulation as the supraspinal components evoke generalized sympathetic discharges which do not depend on the level of afferent input

The VFT was decreased to a similar extent by stimulation at low or high frequency Johansson found that low frequency low intensity stimulations of somatic nerves in baroreceptor denervated cats produced depressor responses which could be attributed to an over all decrease in sympathetic activity Koizumi and Brooks have suggested that the inhibitory component of somatosympathetic reflexes may be responsible for the net decrease in sympathetic nerve activity when somatic nerves are stimulated at low frequency In intact cats it has been found that stimulation of somatic nerves produces transient pressor and depressor responses In the present study the changes in arterial pressure were often transient (especially the low intensity stimulations) and the determination of the VFT was initiated after baroreceptor compensation for the responses was nearly complete (2 minutes) In all cases regardless of the frequency and intensity of stimulation it appears that following cardiovascular compensation for the altered pressure the sympathetic activity to the heart was elevated during somatic nerve stimulations This may indicate that in chloralose-urethane anesthetized dogs with the chest open the excitatory influence on the cardiac sympathetic nerves predominates over the inhibitory component of somatosympathetic reflexes and that increased cardiac sympathetic activity is favored during prolonged stimulation of somatic nerves at both low and high frequencies

That an increased cardiac sympathetic activity was probably responsible for the changes in VFT seen in this study was shown by the failure of somatic nerve stimulation to lower VFT after administration of propranolol The dose of propranolol used in this study has been reported to provide nearly 100 per cent beta adrenergic blockade Stimulation of somatic nerves has been shown to elicit a withdrawal of parasympathetic tone to the heart however administration of a muscarinic blocking dose of atropine

repeated at 30 minute intervals Similarly none of the control VFTs differed significantly within any of the experimental series in this study Since the VFT in the initial control series and control VFTs in subsequent experiments did not change with time it appears that the technique of VFT determination used in this study did not induce changes within the heart which would alter VFT

The VFTs obtained in this study were somewhat lower than commonly reported in the literature in which a similar train of pulses was used in open chested animals[1, 18] This may be accounted for by several factors Most investigators have used pentobarbital anesthesia, while in this study chloralose-urethane an anesthetic combination which probably increases overall sympathetic activity was used However as the per cent decrease in VFT produced during nerve stimulation was similar to the per cent change reported during stimulation of cardiac sympathetic nerves,[8, 11] it is unlikely that increased sympathetic tone was the only reason for the low VFT

Probably the most important factor was that the 310 msec train of pulses extended well beyond the effective refractory period of the ventricles at the pacing frequency of 180 beats/min The consequence of this is that the VFT measured was probably the VFT of one of the evoked premature beats initiated by the train of pulses The ECG showed that many ectopic beats were initiated at current intensities well below the VFT It is well documented that the VFT of ectopic beats is significantly lower than that obtained for normal or paced beats[1] Since the conditions were the same for both control and experimental determinations the comparisons between the various groups should still be valid

In many of the studies reported in the literature concerning somatosympathetic reflexes and effector organ responses the afferent fibers involved are frequently assumed to belong to one or another class of fibers based on a relationship between stimulus intensity and motor threshold Since there is much discrepancy in the literature as to the thresholds of afferent fibers in different nerve trunks, compound action potentials were analyzed to determine the contribution of the various fibers to the changes in VFT measured in this study It was found that Group I fibers in the median tibial, and obturator nerves were activated at a stimulus intensity of 1 × MT Group II fibers at 2 × MT and Group III fibers at 5 × MT Group IV fibers were activated in the median nerve at a stimulus intensity of 10 × MT

The response threshold voltage (about 6 volts) of the sural nerve was taken as the minimal voltage which produced a measurable change either in heart rate or arterial blood pressure No Group I activity was detected in the compound action potentials of this nerve since the sural nerve is primarily a cutaneous sensory nerve and probably does not contain Group I fibers[2] The sural nerve was stimulated at 5 and 10 × RT both of which through compound action potential analysis were found to activate Groups II to IV afferent fibers

Karl and colleagues found that a maximum response could be evoked in sympathetic nerves by stimulation of Group II afferent fibers Janig and associates[1] found that stimulation of Group III afferents in cats increased the sympathetic nerve response to Group II afferent stimulation only slightly In the present study analysis of the compound action potentials of median nerve stimulations revealed that four types of afferent fibers could be stimulated by varying the intensity of stimulation Stimulation of Groups I and II in the median nerve did not evoke a maximal decrease in the VFT as there was a further significant decrease in VFT when Group III fibers were also stimulated Stimulation of the median nerve at 10 × MT activated Groups I to IV afferent fibers but no further decrease in the VFT was seen

It has been reported that stimulation of Group I afferent fibers produces a sympathetic response only under special conditions[5] Since stimulation of the median nerve at 2 × MT activated only Groups I and II the VFT data indicate that stimulation of Group II afferent fibers produced substantial increases in sympathetic nerve activity to the heart Concurrent stimulation of Group III afferents produced an additional increase in sympathetic activity as seen by the further decrease in VFT Increasing the stimulus intensity to include Group IV afferents did not apparently add to the change in sympathetic activity These findings are in agreement with those of Sato and Schmidt,[8] in that Groups II and III were found to elicit large somatosympathetic reflex responses but Group IV stimulations produced

does not alter the VFT from control values (unpublished observation) Therefore, decreased parasympathetic influence was probably not involved in these studies This is not surprising since the degree of vagal tone in a chloralose-urethane anesthetized dog with the chest open is probably minimal [7] Similarly a change in arterial blood pressure does not directly influence the VFT [10] and could not explain the results obtained in this study

Summary

The data indicate that activation of somatic afferent fibers can produce a change in cardiac sympathetic activity which may influence development of arrhythmias under certain conditions In this study the VFT was lowered significantly by stimulation of somatic afferent fibers belonging to Groups II to IV The decrease in VFT was probably due to increased sympathetic activity to the heart since β adrenergic blockade prevented the change in VFT during nerve stimulation

Recently Theroux and associates have shown that premedication of conscious dogs with morphine prevents the occurrence of ventricular fibrillation in the first few minutes following abrupt coronary artery occlusion It was thought that morphine prevented the excitement reaction (which was characterized by 'marked agitation and struggling) in response to the ischemic pain associated with the coronary occlusion According to the present study morphine may have interrupted the somatosympathetic reflex associated with the pain and excitement and prevented the reflex increase in sympathetic activity to the heart These observations deserve further study especially with regard to the effect of morphine on somatosympathetic reflexes An alternate explanation is that morphine may have produced an increase in vagal efferent activity which has been shown to antagonize the influence of the sympathetic nervous system on the heart [3]

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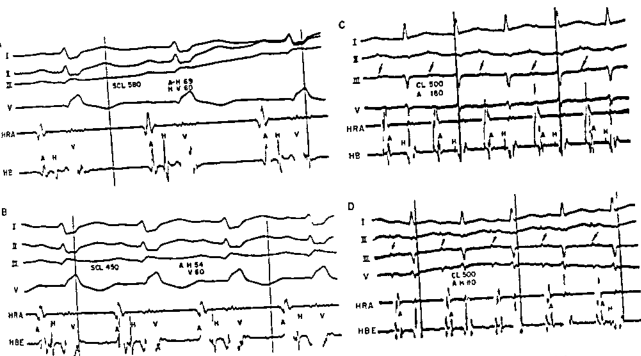


Fig 1 Demonstration of changes in A H interval pre and post Δ 9 THC during sinus rhythm and atrial driving Shown are electrocardiographic Leads I II III and V a bipolar intracardiac high right atrial electrogram *(HRA)* and a His bundle electrogram *(HBE)* *A* is the low right atrial electrogram His bundle potentials are labeled as *H* Atrial pacing spikes are *labeled with arrows* Paper speed is ?00 mm /sec in *A* and *B* 100 mm /sec in *C* and *D* and time lines are at one second intervals in this and subsequent illustrations. The sinus cycle length driven cycle length and electrophysiologic intervals are listed on each panel *Panels A* (before Δ 9 THC) and *B* (after Δ 9-THC) show the effect of Δ 9 THC on sinus cycle length and A H interval during normal sinus rhythm (patient 1) *Panels C* (pre) and *D* (post) show the effect of Δ 9 THC on A H interval at equivalent driven cycle length (patient 2)

Table I Effect of Δ 9 THC on sinoatrial function

Pt. no	Sinus Cycle length (msec)		SRT (msec)		Max SRT (msec)		Calculated SACT (msec)		PA (msec)		Atrial Refractory Periods: Sinus rhythm: AERP (msec)		AFRP (msec)		Driving at identical CL: Driving CL (msec)	AERP (msec)		AFRP (msec)	
	C	THC	C	THC	C	THC	C	THC	C	THC	C	THC	C	THC		C	THC	C	THC
1	580	450	742	550	800	550	82	47	27	24	160	140	240	?30	430	230	140	230	200
?	960	545	1040	560	1240	640	35	15	43	46	230	190	3?0	230	470	210	1,0	250	200
3	00	580	1010	600	11?0	6"0	90	60	25	25	160	160	260	235	500	15o	160	220	210
4	580	460	660	530	730	610	75	55	25	18	240	230	260	?60	440	220	2?0	240	230
5	960	,30	1?17	790	1340	850	81	68	25	26	240	250	3?0	300	600	260	250	280	300
6	930	615	988	6 0	11 0	8?0	97	89	30	30	240	210	.60	210	667	2?0	220	290	300

Abbreviations AERP = trial ffecti refract ry period AFRP = atrial funct o l refractory period C = co trol CL = cycle length Max = max im m msec = m llisec nd Pt. No = patient number SACT = sino trial c d t n tim SRT = sinus nod recovery time THC = Δ 9 tetrahydroc nabin l (nabis)

neous electrocardiographic Leads I II III and V were recorded

Atrial pacing was performed at increasing rates in 10 beat/minute increments until A V nodal Wenckebach periods were observed Sinus node recovery time was defined as the interval between the last paced P wave to the first spontaneous P wave after sudden cessation of pacing at a rate of 130/minute [3] Three sinus recovery times were determined at this rate and were then averaged in each patient Maximum sinus node recovery time was defined as the longest asystolic period after

The electrophysiological effects of delta-9-tetrahydrocannabinol (cannabis) on cardiac conduction in man

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Studies concerning the cardiovascular effects of marijuana in man are limited to effects on heart rate non invasive indices of cardiac performance, and peripheral arterial blood pressure and blood flow [1, 5] We have recently reported in man that acute intravenous administration of levo delta 9 tetrahydrocannabinol (Δ 9 THC) the pharmacologically active substance in marijuana,[6, 9] enhanced cardiac performance as suggested by shortening of preejection period and prolongation of corrected left ventricular ejection time [5] Information regarding the effects of Δ 9 THC on electrical activity of the heart is limited to electrocardiographic observations concerning S T segments and T waves [1, 3, 10, 1]

In the present study we have used His bundle recording and cardiac stimulation to systematically examine the effects of intravenous Δ 9 THC on cardiac conduction in man Our results suggest that Δ 9 THC enhances sinus nodal automaticity and facilitates sinoatrial and A V nodal conduction Δ 9 THC had no significant effect on atrial or intraventricular conduction

Methods

The study group consisted of six patients undergoing diagnostic electrophysiological evaluation because of intraventricular conduction disease (patients 1 to 5) and suspected supraventricular arrhythmia (patient 6) who volunteered for this protocol All were males with ages ranging from 18 to 45 years (mean ± SEM 33 ± 4 6 years) All patients were studied in the non sedated, postabsorptive state after written informed consent had been obtained No patient was taking medication prior to the study Patients were screened for latent psychiatric disease prior to being accepted for study [5]

His bundle electrograms were recorded using a tripolar catheter passed percutaneously via a femoral vein [1] A quadripolar catheter was positioned in the high right atrium at the superior vena caval junction for atrial stimulation and recording Recordings were obtained on a multichannel oscilloscopic photographic recorder* at paper speeds of 100 and 200 mm /sec Simulta

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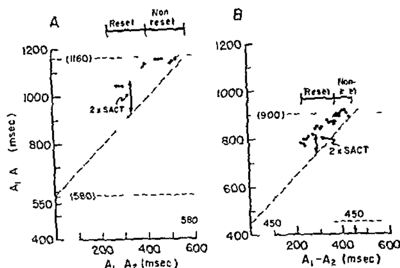


Fig 3 Graphic representation of sinus node responses and zones to extrastimulus during sinus rhythm in patient 1 A A intervals (ordinate) are plotted as a function of A A intervals (abscissa) in msec Panel A is before Δ 9 THC The sinus cycle is 580 msec The zone of non reset due to interference ranges from 580 to 410 msec The zone of reset is between 400 and 240 msec The sinoatrial conduction time (SACT) is 8? msec Panel B is after Δ 9 THC The sinus cycle is 450 msec The zone of non reset ranges from 450 to 370 msec and the zone of reset is between 360 and 230 msec The sinoatrial conduction time is 47 msec

Table II Effect of Δ 9 THC on A V nodal and intraventricular conduction

Pt no	A H (msec)		A H at equiv CL (msec)			Paced atrial rate producing 2 A V block (beats/min)		A V nodal refractory periods: Sinus rhythm: AVN ERP (msec)		AVN FRP (msec)		Driving at Identical CL: Driving CL (msec)	AVN ERP (msec)		AVN FRP (msec)		H V (msec)	
	C	THC	CL	C	THC	C	THC	C	THC	C	THC		C	THC	C	THC	C	THC
1	69	›4	430	95	55	190	210	340	240	390	280	430	340	240	380	280	60	60
2	74	65	500	180	110	180	200	310	240	430	340	470	290	2?0	380	3?0	34	31
3	7?	?0	545	100	70	200	210	290	250	370	320	?00	340	260	370	310	38	36
4	7?	75	430	8?	85	190	190	260	250	350	300	440	240	230	330	320	34	32
5	88	73	667	130	?0	110	160	330	3?0	490	440	600	430	360	570	470	39	40
6	105	90	–	–	–	110	160	4?0	3?0	530	410	667	560	3?0	580	460	31	32

Abbreviations AVN ERP = A V nodal effective refractory period AVN FRP = A V nodal functional refractory period C = control CL = cycle length Equiv = equivalent msec = millisecond Pt No = patient number THC = Δ 9-tetrahydrocannabinol (cannabis)

with a mean of 56 ± 9 7 msec ($p < 0 005$) (Fig 3) Calculated sinoatrial conduction time decreased in all six patients after Δ 9 THC

Intra atrial conduction (Tables I and III) P A intervals ranged from 25 to 43 msec with a mean of 29 ± 2 9 msec during the control state After Δ 9 THC the P A intervals ranged from 18 to 46 msec with a mean of 28 ± 3 9 msec (NS) Atrial effective and functional refractory periods were measured in all patients during sinus rhythm and at an equivalent driven cycle length During sinus rhythm the atrial effective refractory period ranged from 160 to 240 msec with a mean of 212 ± 16 4 msec After Δ 9 THC the atrial effective refractory period ranged from 140 to 2?0 msec with a mean of 197 ± 17 msec (NS) The atrial functional refractory period ranged from 240 to 360 msec with a mean of 293 ± 19 msec prior to and 230 to 300 msec with a mean of 261 ± 14 7 msec after Δ 9 THC administration (NS) At identical driven cycle lengths (mean 518 msec) atrial effective refractory period ranged from 155 to 260 msec with a mean of 216 ± 14 msec before and 140 to 250 msec with a mean of 193 ± 17 4 msec after Δ 9 THC (NS) The atrial functional refractory period ranged from 220 to

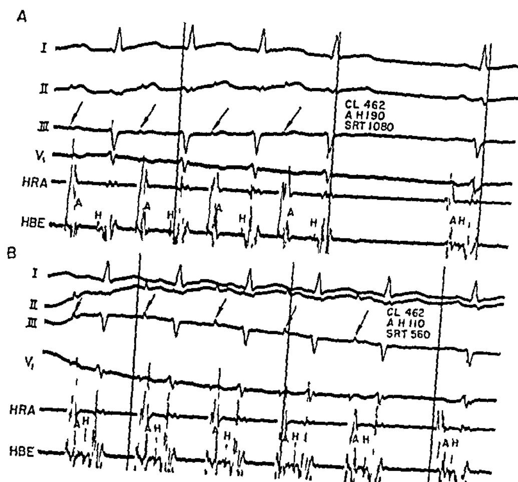


Fig 2 Patient 2 Sinus node recovery time *(SRT)* before *(A)* and after *(B)* the administration of Δ 9 THC The paced cycle length *(CL)* and SRT are listed

sudden cessation of pacing at any of the tested heart rates A cycle length approximately 25 to 35 per cent faster than the sinus rate was utilized so that refractory periods could be measured at identical cycle lengths before and after infusion of Δ 9 THC Antegrade conduction intervals refractory periods and sinus nodal responses were defined and measured as previously described [13-15] Sinoatrial conduction time was calculated as described by Strauss and co workers [16]

After control values were obtained, 25 mcg / kg of Δ 9 THC was administered intravenously which for a 75 to 80 kilogram person is the dose equivalent to smoking one marijuana cigarette containing 5 mg Δ 9 THC [5] Electrophysiological studies were initiated five minutes after the infusion and lasted a total of approximately 25 minutes, a time interval corresponding to peak effect of intravenous Δ 9 THC [5] Student s paired t test was used to analyze the statistical significance of data

Results

Effects on sinus node (Tables I and III) Sinus cycle lengths ranged from 580 msec to 960 msec, with a mean ± SEM of 785 ± 76 msec After Δ 9 THC sinus cycle lengths ranged from 450 msec to 730 msec, with a mean of 563 ± 42 msec ($p < 0.01$) (Figs 1A and 1B) Sinus cycle lengths decreased in all patients Sinus node recovery time (at a paced rate of 130/minute) ranged from 660 to 1 217 msec with a mean recovery time of 943 ± 84 msec during the control state After Δ 9 THC administration recovery times ranged from 530 to 790 msec with a mean of 617 ± 40 msec ($p < 0.005$) (Fig 2) Sinus node recovery times decreased in all patients Maximum sinus node recovery times ranged from 730 to 1,340 msec before Δ 9 THC with a mean of 1 060 ± 99 msec After Δ 9 THC, maximum sinus node recovery times ranged from 550 to 850 msec with a mean of 690 ± 49 msec ($p < 0.005$) Maximum sinus recovery times decreased in all patients

The effect of Δ 9 THC on calculated sinoatrial conduction time was evaluated in all patients during the control state and after drug infusion The sinoatrial conduction time during the control state ranged from 35 to 97 msec, with a mean of 77 ± 8.9 msec After Δ 9 THC administration, the conduction time ranged from 15 to 89 msec

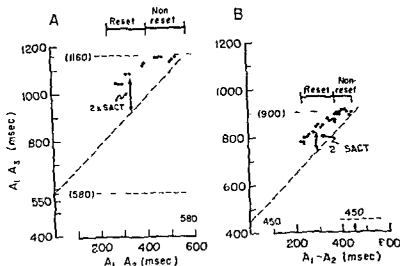


Fig 3 Graphic representation of sinus node responses and zones to extrastimulus during sinus rhythm in patient 1 A A intervals *(ordinate)* are plotted as a function of A A intervals *(abscissa)* in msec *Panel A* is before Δ 9 THC The sinus cycle is 580 msec The zone of non reset due to interference ranges from 580 to 410 msec The zone of reset is between 400 and 240 msec The sinoatrial conduction time (*SACT*) is 82 msec *Panel B* is after Δ 9 THC The sinus cycle is 450 msec The zone of non reset ranges from 450 to 3 0 msec and the zone of reset is between 360 and 230 msec The sinoatrial conduction time is 47 msec

Table II Effect of Δ 9 THC on A V nodal and intraventricular conduction

Pt. no	A H (msec)		A H at equiv CL (msec)			Paced atrial rate producing 2 A V block (beats/min)		A V nodal refractory periods: Sinus rhythm: AVN ERP* (msec)		Sinus rhythm: AVN FRP (msec)		Driving at Identical CL: Driving CL (msec)	AVN ERP (msec)		AVN FRP (msec)		H V (msec)	
	C	THC	CL	C	THC	C	THC	C	THC	C	THC		C	THC	C	THC	C	THC
1	69	54	430	95	55	190	210	340	240	390	280	430	340	240	380	280	60	60
2	74	65	500	180	110	180	200	310	240	430	340	470	290	250	380	370	34	31
3	75	70	545	100	70	200	210	290	250	3?0	320	500	340	260	370	310	38	36
4	5	75	430	85	85	190	190	?60	250	350	300	440	240	230	330	320	34	32
5	88	73	667	130	70	110	160	330	3?0	490	440	600	430	360	5?0	470	39	40
6	105	90	—	—	—	110	160	450	3?0	530	410	667	560	370	580	460	31	3?

Abbreviations AVN ERP = A V odal effecti e ref actory period AVN FRP = A V nod l functional refractory peri d C = control CL = cycle length Equiv = eq valent msec = millisecond Pt No = patient numb THC = Δ 9-tetrahydrocannabinol (cannabis)

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Table III Summary of electrophysiologic findings after administration of Δ 9 THC

	N	State	Mean ± SEM	p value
Sinus cycle length (msec)	6	C	785 ± 76	< 0 01
		THC	563 ± 42	
SRT (msec)	6	C	913 ± 84	< 0 005
		THC	617 ± 40	
Max SRT (msec)	6	C	1060 ± 99	< 0 005
		THC	690 ± 49	
SACT (msec)	6	C	77 ± 8 9	< 0 005
		THC	56 ± 9 7	
P A interval (msec)	6	C	29 ± 2 9	NS
		THC	28 ± 3 9	
Atrial ERP (msec) (NSR)	6	C	212 ± 16 4	NS
		THC	197 ± 17	
Atrial FRP (msec) (NSR)	6	C	293 ± 19	NS
		THC	261 ± 14 7	
Atrial ERP (msec) (during atrial driving)	6	C	216 ± 14	NS
		THC	193 ± 17 4	
Atrial FRP (msec) (during atrial driving)	6	C	252 ± 11 4	NS
		THC	240 ± 19 5	
A H Interval (msec) (NSR)	6	C	81 ± 5 4	< 0 02
		THC	71 ± 4 9	
A H Interval at equivalent cycle length (msec)	5	C	118 ± 17 2	< 0 05
		THC	78 ± 9 3	
Paced atrial rate producing 2 A V block (beats/min)	6	C	163 ± 17	< 0 05
		THC	188 ± 9 4	
A V nodal ERP (msec) (NSR)	6	C	330 ± 26 7	< 0 05
		THC	270 ± 15 9	
A V nodal FRP (msec) (NSR)	6	C	427 ± 28 9	< 0 005
		THC	348 ± 25 9	
A V nodal ERP (msec) (during atrial driving)	6	C	367 ± 46 4	< 0 025
		THC	285 ± 25 6	
A V nodal FRP (msec) (during atrial driving)	6	C	433 ± 43 9	< 0 02
		THC	368 ± 32 8	
H V interval (msec)	6	C	39 ± 4 3	NS
		THC	38 ± 4 5	

Abbreviations C = control ERP = effective refractory period FRP = functional refractory period Max = maximum msec = millisecond N = number of patients NS = not significant SACT = sinoatrial conduction time SEM = standard error of the mean SRT = sinus node recovery time THC = Δ 9 tetrahydrocannabinol (cannabis) NSR = normal sinus rhythm

290 msec with a mean of 252 ± 11 4 msec prior to and 200 to 300 msec with a mean of 240 ± 19 5 msec after Δ 9 THC (NS)

A V nodal conduction (Tables II and III) A H intervals ranged from 69 to 105 msec with a mean of 81 ± 5 4 msec during control sinus rhythm After Δ 9 THC administration A H intervals ranged from 54 to 90 msec with a mean of 71 ± 4 9 msec ($p < 0 02$) (Figs *1A* and *1B*)

With atrial pacing, A H intervals at equivalent paced rates were measured in five patients The mean A H interval at an equivalent paced heart rate (140 beats/minute in two patients 120 beats/minute, 110 beats/minute and 90 beats/minute in the remaining three patients respectively) was 118 ± 17 2 msec before and 78 ± 9 3 msec after Δ 9 THC ($p < 0 05$) (Figs *1C* and *1D*) The paced rate at which A V nodal Wenckebach periods proximal to the His bundle occurred was noted in all patients The mean rate was 163 ± 17 msec before and 188 ± 9 4 msec after the infusion of Δ 9 THC ($p < 0 05$) During sinus rhythm, A V nodal effective refractory periods ranged from 260 to 450 msec with a mean of 330 ± 26 7 msec before and ranged from 240 to 320 msec with a mean of 270 ± 15 9 msec after Δ 9 THC ($p < 0 05$) A V nodal functional refractory periods ranged from 350 to 530 msec with a mean of 427 ± 28 9 msec prior to and ranged from 280 to 440 msec with a mean of 348 ± 25 9 msec following the administration of Δ 9 THC ($p < 0 005$) A V nodal effective and functional refractory periods during sinus rhythm and atrial pacing were decreased in all patients after Δ 9 THC

At identical driven cycle lengths, A V nodal effective refractory periods ranged from 240 to 560 msec with a mean of 367 ± 46 4 msec before and ranged from 230 to 370 msec with a mean of 285 ± 25 6 msec after drug administration ($p < 0 025$) (Fig 4) The A V nodal functional refractory period ranged from 330 to 580 msec with a mean of 433 ± 43 9 msec prior to and ranged from 280 to 470 msec with a mean of 368 ± 32 8 msec following drug administration ($p < 0 02$) (Fig 4)

Intraventricular conduction (Tables II and III) H V intervals ranged from 31 to 60 msec with a mean of 39 ± 4 3 msec before and ranged from 31 to 60 msec with a mean of 38 ± 4 5 msec after Δ 9 THC infusion (NS) (Figs *1A* and *1B*) The effective refractory period of the ventricular specialized conduction system was measured in only one patient During sinus rhythm and during atrial driving the effective refractory period of the VSCS was 380 msec and 320 msec prior to and 370 msec and 320 msec after Δ 9 THC respectively

Arrhythmias Frequent multifocal premature ventricular contractions were noted after Δ 9 THC administration in one patient which disap

peared 15 minutes following cessation of drug infusion (patient 3) No other dysarrhythmias were noted

Discussion

Frequent use of marijuana among young adults had led to several recent investigations evaluating the pharmacological effects of this agent on the cardiovascular system [1,5,17,8] These studies demonstrated that marijuana or Δ 9 THC increased sinus rate and cardiac performance as suggested by a decrease in pre ejection period and increase in left ventricular ejection time [1, 0, 12, 19, 2] However data concerning the effects of Δ 9 THC on cardiac conduction other than heart rate are limited

The effect of Δ 9 THC on heart rate has been well studied in animals In an experimental study Cavero and associates demonstrated that Δ 9 THC caused significant decrease in rate in anesthetized dogs There was a linear decrease in heart rate with increasing doses of Δ 9 THC the rate decreasing by 10 ± 3 beats/minute with 39 mcg /Kg dose of Δ 9 THC by 33 ± 5 beats/minute with 312 mcg /Kg and by 42 ± 6 beats/minute with a dose of 2 5 mg /Kg of Δ 9 THC After bilateral vagotomy and stellate ganglia ablation Δ 9 THC failed to decrease the heart rate suggesting that this effect of Δ 9 THC was mediated through the autonomic nervous system Similar results were reported in cats and rats by Graham and Li who used atropine and propranolol for autonomic denervation Bright and co workers[11] demonstrated in dogs that bradycardia produced by Δ 9 THC could not be completely prevented by vagotomy alone indicating that action was mediated through both the sympathetic and parasympathetic nervous system

Considerable data are available concerning the effect of Δ 9 THC on heart rate in man [1,5] These studies indicated that contrary to animal data Δ 9 THC in man caused significant increase in heart rate Beaconsfield and co workers[3] demonstrated an increase in mean heart rate of 23 beats/minute immediately after six volunteers smoked a cigarette containing marijuana In the same study they also demonstrated that marijuana induced tachycardia could be prevented by orally administered propranolol and tachycardia could still be induced with marijuana even after subcutaneous

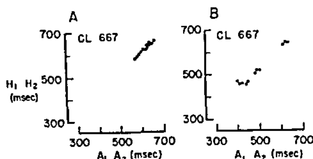


Fig 4 Patient 6 Atrioventricular conduction curves pre *(A)* and post *(B)* administration of Δ 9 THC A A intervals are plotted on the abscissa and H H intervals are plotted on the ordinate The driving cycle length is 667 msec in both Control effective and functional refractory periods of the A V node are 560 and 580 msec., respectively *(Panel A)* After Δ 9 THC the effective and functional refractory periods of the A V node are decreased to 370 and 460 msec respectively *(Panel B)*

administration of 0 6 mg of atropine These observations suggested that increase in heart rate was mediated through beta adrenergic stimulation Similar results were also reported by Bright and associates [4] and Weiss and colleagues [2] The latter workers demonstrated increased urinary excretion of epinephrine after use of Δ 9 THC confirming sympathetic stimulation with this agent The results of the present study are in agreement with the previous investigations We demonstrated a 39 per cent increase in the mean sinus rate following Δ 9 THC administration in our patients

In a recent experimental study Beaconsfield and associates [5] using anesthetized rats and guinea pigs demonstrated sinoatrial block induced by larger doses (> 100 mcg /Kg) of Δ 9 THC This observation suggested that Δ 9 THC increased perinodal refractoriness The results of the present study suggest that Δ 9 THC in man facilitates conduction through the perinodal fibers as manifested by an average 27 per cent decrease in calculated sinoatrial conduction time following drug administration Shortening of sinus cycle length would not explain this change since calculated sinoatrial conduction time prolongs with spontaneous decrease in cycle length The abbreviation of sinus recovery time noted in our patients is probably related to both facilitation of perinodal fiber conduction and enhancement of sinus automaticity by Δ 9 THC

It has been reported that higher doses of Δ 9 THC (> 100 mcg /Kg) could induce transient

P R prolongation and/or second degree A V block (both Types I and II) in intact experimental animals [5] In the present study, contrary to the previous animal experimentation, we demonstrated significant facilitation of A V nodal conduction as suggested by decrease in A H interval and A V nodal refractoriness Intra atrial and intraventricular conductions were unaffected by Δ 9 THC in our patients

Development of premature ventricular contractions (enhanced ventricular automaticity) with Δ 9 THC has been reported by many workers Johnson and Domino[1] have shown an increase in ventricular automaticity in two of 15 normal subjects following Δ 9 THC In one of seven patients reported by Kochar and Hosko,[11] multiple premature ventricular contractions occurred after Δ 9 THC administration Roth and co workers[10] reported infrequent occurrence of premature ventricular beats in three of ten patients with Δ 9 THC In one of our patients ventricular ectopy was noted following drug administration

From the previous experimental and human studies, it is not clear whether the cardiovascular effects of Δ 9 THC are mediated by increased sympathetic activity and/or vagal inhibition The results reported by Beaconsfield and associates[3] and Bright and colleagues[4] suggested that the effects of Δ 9 THC were mediated by beta sympathetic stimulation In a recent study from our laboratory[5] it was shown that beta blockade partially ablated the changes in heart rate left ventricular ejection time and Q 2 interval observed with Δ 9 THC

The electrophysiological effects of Δ 9 THC in this study are similar to those recently described with both isoproterenol and atropine [7, 8] Both drugs increased sinus rate decreased sinus recovery time and facilitated A V nodal conduction We would postulate that the electrophysiological effects of Δ 9 THC in man are probably centrally mediated through the autonomic nervous system[5] Further studies utilizing beta blockade and atropine in patients would further clarify the mechanism of action of Δ 9 THC on cardiac conduction

In conclusion acute intravenous administration of Δ 9 THC in a dose approximating that delivered by one marijuana cigarette markedly enhanced sinus automaticity and facilitated sinoatrial and A V nodal conduction The clinical significance (therapeutic or deleterious) of these pharmacologic effects needs further evaluation

Summary

Electrophysiologic studies were performed in six patients before and after administration of 25 mcg /Kg of intravenous delta 9 tetrahydrocannabinol (Δ 9 THC) The mean ± SEM sinus length was 785 ± 76 msec prior to and 563 ± 42 msec after THC ($p < 0.01$) The mean sinus node recovery and maximum sinus node recovery times were respectively 943 ± 84 msec and 1060 ± 99 msec before and 617 ± 40 msec and 690 ± 49 msec after THC ($p < 0.005$ and < 0.005) Mean calculated sinoatrial conduction time was 77 ± 8 9 msec before and 56 ± 9 7 msec after THC ($p < 0.005$) Mean A H intervals during sinus rhythm before and after THC were 81 ± 5 4 and 71 ± 4 9 msec respectively ($p < 0.02$) and 118 ± 17 2 msec and 78 ± 9 3 msec at equivalent driven cycle length ($p < 0.05$) The mean paced atrial rates producing second degree block proximal to the His bundle before and after THC were respectively, 163 ± 17 and 188 ± 9 4 beats/minute ($p < 0.05$) Mean A V nodal effective and functional refractory periods at equivalent driven cycle length were respectively 367 ± 46 4 msec and 433 ± 43 9 msec before and 285 ± 25 6 msec and 368 ± 32 8 msec after THC ($p < 0.025$ and < 0.02) Mean H V interval was 39 ± 4 3 msec prior to and 38 ± 4 5 msec after THC (NS)

In conclusion Δ 9 THC produces a potent effect on the heart, probably centrally mediated through the autonomic nervous system with markedly enhanced sinus automaticity and facilitation of sinoatrial and A V nodal conduction The clinical significance (therapeutic or deleterious) of these pharmacological effects needs further evaluation

We greatly appreciate the secretarial help of Mrs Julia V Cancel

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Spatial and temporal heterogeneity of left ventricular perfusion in awake dogs

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In the past when only total left ventricular blood flow could be measured, it was assumed that the perfusion of the left ventricular myocardium was homogenous Recent studies with tracer microspheres[1-5] have shown that blood flow to large regions of the left ventricle is relatively evenly distributed, but perfusion to small left ventricular segments is heterogeneous Two types of heterogeneity have been described spatial heterogeneity and temporal heterogeneity Spatial heterogeneity is variation in perfusion to small segments of the left ventricle at the same time Temporal heterogeneity is variation in perfusion to a single small segment with time that occurs even though total coronary flow remains constant Thus far, all investigations that have demonstrated spatial and temporal heterogeneity of perfusion have been done in anesthetized open chest dogs or in isolated perfused hearts[1-5] In these studies anesthesia surgical trauma and the accompanying hemodynamic alterations may have contributed to or been responsible for the heterogeneity of the left ventricular perfusion previously observed The purpose of this study was to quantitate spatial and temporal heterogeneity of left ventricular perfusion in awake animals under near basal conditions

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Methods

General plan All studies were performed in awake chronically instrumented dogs Myocardial perfusion was measured in 96 segments of the left ventricle with labelled microspheres Spatial heterogeneity of perfusion was assessed in all dogs by quantifying the variability of perfusion to small segments of the myocardium observed during a single injection of microspheres To determine the inherent error in the microsphere measurements three or four differently labelled batches of microspheres were injected simultaneously in one group of dogs To study temporal heterogeneity of perfusion three of four batches of differently labelled microspheres were injected sequentially at one minute intervals in a second group of dogs By comparing the results of simultaneously injected and sequentially injected microspheres in the two groups of animals the true magnitude of temporal heterogeneity could be quantified

Surgical procedures Twenty four mongrel dogs of both sexes weighing between 18 and 30 kilograms were anesthetized with sodium pentobarbital (25 mg /Kg intravenously) and ventilated with room air by an endotracheal tube and a Harvard respirator Under sterile conditions the

left chest was opened and a polyethylene cannula (I D = 0 085 inch) was placed in the left atrium and a polyethylene cannula (I D = 0 006 inch) was placed in the descending aorta via the left internal mammary artery In some dogs pacing wires were sewn to the right atrium The cannulas were filled with heparin (7 000 units/ml) capped and the proximal ends along with the pacing wires were brought out onto the chest wall and placed subcutaneously Antibiotics were given during the first three postoperative days Seven to ten days after surgery the dogs were studied

Measurement of myocardial perfusion Microspheres 15 ± 5 μ in diameter labeled with ^{3}I or microspheres 7 to 10 μ in diameter labeled with CR ^{6}Sc ^{85}Sr and ^{1}Ce were used For each flow measurement between 1 7 by 10 and 16 6 by 10^{6} tracer microspheres were suspended in saline and injected into the left atrium Before injection the vial containing the microspheres and one drop of Tween 80 was mechanically agitated for at least 4 minutes Microscopic examination of microspheres prepared in this manner showed dispersion of at least 98 per cent of the spheres Occasionally small groups of three to five spheres were observed The microspheres were injected over a 15 second period and the cannula was flushed over a 30 second period with 5 ml of saline at 37 C Starting 1 minute before injection and continuing until 3 minutes after injection blood was withdrawn from the cannula in the descending aorta at a rate of 2 06 ml per minute with a Harvard pump In the sequentially injected dogs blood was withdrawn continuously from 1 minute before injection until 3 minutes after the last injection of microspheres

Following completion of the study the dogs were anesthetized with sodium pentobarbital (25 mg/kg intravenously) and subsequently killed with intravenous potassium chloride The heart was excised and the free walls of the right ventricle left atrium great vessels valves surface vessels and epicardium fat were removed Using the posterior descending coronary artery as the starting point the left ventricle was divided into four levels of 8 segments each and each segment was divided into three layers—endocardium mid wall and epicardium The thickness of these layers was approximately equal Thus the left ventricle was divided into 96 segments The relative geometric position of each segment was constant from animal to animal [4] The myocardial segments were weighed placed in plastic tubes and counted for 5 minutes in a three inch well type sodium iodide gamma counter The average weight of the segments was 1 08 ± SE 0 03 g Reference blood samples were divided so that their counting geometry was similar to that of the myocardial samples Isotope separation was done using standard techniques

Myocardial blood flow was calculated using the formula MBF = C_m × 100 × RBF − C where *MBF* = myocardial blood flow in ml per minute × 100 g C_m = counts per gram of myocardium *RBF* = reference blood flow (rate of withdrawal from the reference artery) and C_r = total counts in the reference blood

Occasionally the flow to a single segment was unusually high (greater than 3 0 standard deviation from the mean perfusion distribution) The number of such segments in each dog averaged 1 56 ± SE 0 6 Since unusually low flows were rare these infrequent high flows may have resulted from a small degree of clumping of the microspheres Therefore these high flows were deleted prior to any further analysis of the data

Experimental protocol On the day of the study the dogs were given 10 mg of morphine sulfate intravenously and then acclimated to the laboratory for at least 1 hour prior to microsphere injection Under lidocaine anesthesia the catheters and the pacing wires were exposed In the dogs studied with sequential microsphere injections a second arterial catheter was placed in the femoral artery under lidocaine anesthesia Blood was withdrawn from the catheters they were flushed with saline and were attached to Statham P23 db strain gauges placed at the level of the mid chest The electrocardiogram and pressure signals were recorded on a multichannel direct writing recorder In twelve dogs arterial P_{O_2} P_{CO_2} and pH were measured several minutes prior to injection of the microspheres

Three groups of dogs were studied Spatial heterogeneity was assessed in twelve dogs by injecting a single batch of microspheres 15 ± 5 μ in diameter labeled with ^{3}I The variance in segmental flow inherent in the microsphere technique was studied by injecting simultaneously three or four differently labeled batches of 7 to 10 μ microspheres into the left atrium of a second

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Surgical procedures Twenty four mongrel dogs of both sexes weighing between 18 and 30 kilograms were anesthetized with sodium pentobarbital (25 mg /Kg intravenously) and ventilated with room air by an endotracheal tube and a Harvard respirator Under sterile conditions the

Table II Spatial heterogeneity of perfusion‡

	Number of dogs	Mean myocardial perfusion (mL/min × 100 g)	Mean dispersion $\left(D = \frac{SD}{\bar{X}} \times 100 \right)$
Group I Single injection of 15 ± 5μ spheres	12	84 ± 12†	19 ± 2
Group II Simultaneous injection of 3-4 batches of 7 10μ spheres	6	87 ± 8	20 ± 1
Group III Sequential injection of 3-4 batches of 7 10μ spheres	6	121 ± 17	25 ± 5

D = dispersion SD = the standard deviation of the myocardial perfusions to the 96 ventricular segments in a single dog and $\bar{X}_{av}$ = mean myocardial perfusion of that perfusion determination
†± 1 SE
‡Spatial heterogeneity expressed as dispersion was similar in the animals studied with 15 ± 5μ spheres or 7 10μ spheres. The weighted average dispersion of all three groups was 21 4 ± 1.5%

sphere technique and temporal heterogeneity were quantified by determining the range of perfusion (highest minus the lowest flow in normalized per cent) to each of the 96 segments observed by injecting three or four groups of differently labeled spheres An average range of segmental perfusion was then calculated for each dog The perfusion data of these two groups of experiments were normalized to eliminate the effects of spatial heterogeneity and intra animal variation in the mean left ventricular perfusion The normalization was done by dividing each segmental flow by the mean flow of the three or four flows of that segment and by the mean perfusion of all 96 segments for each flow determination × 100 The difference in the average normalized range of perfusion in the simultaneously and sequentially injected dogs was compared with an unpaired t test All results were expressed as the mean ± 1 standard error

Results

Hemodynamics and average left ventricular perfusion Table I shows the average heart rate systemic pressure left atrial pressure and left ventricular perfusion observed in the three groups of animals in this study Blood gases were measured in group I and the average Po_2 Pco_2 and pH values were 81 ± 2 mm Hg 33 ± 1 mm Hg and 7 4 ± 0 01 mm Hg respectively

The distribution of flow to large regions of the left ventricle (base to apex lateral wall to septum) was relatively evenly distributed The apex received about 8 per cent more flow per gram than the three other levels and endocardium received more flow per gram than the epicardium A similar observation has previously been reported from our laboratory The average endocardium/epicardium ratio was 1 35 ± 0 02 and

Table III Mean flows for simultaneous and sequential flows*

Simultaneous mean flows (ml/min × 100 g)†				
Dog no	Flow one	Flow two	Flow three	Flow four
13	85 5	83 8	82.3	(ND)‡
14	77.2	83 8	88 1	84 6
15	118 5	130 3	117 6	112 0
16	64.5	6? 1	64.2	69 1
17	73 0	75 0	69 1	?0 4
18	140 4	113 8	124 3	(D)§

Sequential mean flows (ml/min × 100 g)				
Dog no	Flow one	Flow two	Flow three	Flow four
19	97 9	93 1	131 9	(D)
20	87 7	6 8	97 3	(D)
21	84 6	125 0	90 0	115 2
22	125 3	143 1	137.3	(ND)
23	149 5	159 1	185 2	(D)
24	188 5	147 1	168 9	(D)

*Mean left ventricular perfusions for the simultaneous and the sequential studies (see text for details)
† = ml. per minute per 100 Gm of myocardium
‡ND = flow not done
§D = flow deleted

was not significantly different in the three groups of animals studied

Spatial heterogeneity The distribution of flow to small left ventricular segments in a single dog is shown in Fig 1 The mean left ventricular perfusion was 62 ml/min × 100 g and one standard deviation of the distribution was about 12 ml/min × 100 g Thus the dispersion of perfusion in this dog was 19 5 per cent

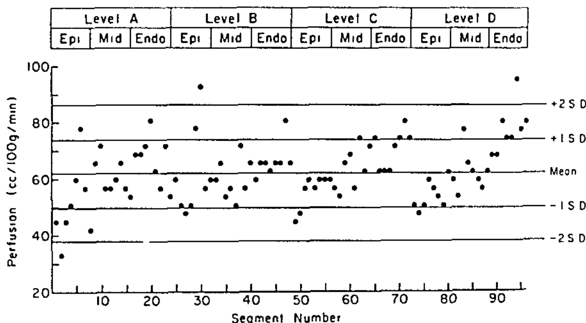


Fig 1 Distribution of individual segmental flows in all 96 segments of dog number 8 The mean flow was 62 1 ml / min × 100 g and the standard deviation was 12 1 ml /min × 100 g Thus the dispersion for this animal was 19 5 per cent (12 1 ÷ 62 1 × 100)

Table I Hemodynamic data and mean myocardial perfusions*

	Number of dogs studied	*Heart rate (beats per min)*	*Mean aortic pressure (mm Hg)*	*Mean left atrial pressure (mm Hg)*	*Mean myocardial perfusion (ml /min × 100g of myocardium)*
Group I Single injection of 15 ± 5μ spheres	12	80 ± 4†	95 ± 4	< 5	84 ± 12
Group II Simultaneous injection of 3 4 batches of 7 10μ spheres	6	92 ± 7	100 ± 5	< 5	87 ± 8
Group III Sequential injection of 3 4 batches of 7 10μ spheres	6	107 ± 1	95 ± 9	< 5	121 ± 17

The mean heart rate aortic pressure and left atrial pressure are shown for the three groups of dogs in this study The faster heart rate and greater myocardial perfusions observed in the sequentially injected dogs were due to pacing this group of dogs at a rate sufficiently high to ensure capture
†± 1 S E

group of six dogs In these studies the differently labeled spheres were mixed and agitated together for 4 minutes prior to injection Temporal heterogeneity of segmental flow was studied by injecting three or four differently labeled batches of 7 to 10 μ microspheres sequentially at 1 minute intervals into the left atrium of a third group of dogs The data from a single flow determination (one of the batches of microspheres) in each of the dogs in the latter two groups was also used to assess spatial heterogeneity so that the effect of sphere size on spatial heterogeneity could be determined

Statistical analysis Spatial heterogeneity to small left ventricular segments was quantified by determining the dispersion of perfusion to individual segments of the left ventricle at one point in time Dispersion was defined as

$$D = \frac{SD_{mp}}{\bar{X}_{mp}} \times 100$$

where D = dispersion SD_{mp} = the standard deviation of the myocardial perfusion to the 96 ventricular segments in a single dog and $\bar{X}_{mp}$ = mean myocardial perfusion of that perfusion determination

Segmental perfusion variance related to the micro

myocardial perfusion of the animals studied are similar to values for these parameters which have been previously reported by other investigators studying awake dogs.[8,9] Although our dogs were slightly sedated and briefly acclimated to the laboratory, no extensive conditioning was undertaken. However, heart rates in dogs well acclimated to the conditions in a laboratory are similar to those reported in this study.[10] Thus, the data indicate that the animals were in a near basal state at the time of the study.

The magnitude of spatial heterogeneity observed (mean dispersion = 20.7 per cent) was similar to what we have previously reported in open chest anesthetized dogs. To a minor extent the spatial heterogeneity observed was due to variation related to the methodology employed since the range of variability introduced by the microsphere technique was about ± 10 per cent (see Fig. 2, simultaneous injections) and the average range of prefusion (± 3 SD) to small segments of the left ventricle at one point in time was ± 62.1 per cent.

Segmental variation in perfusion that is time dependent (temporal heterogeneity) can only be demonstrated if hemodynamics and left ventricular perfusion are held constant during the time that the data are collected. In this study, in the sequentially injected dogs, heart rate, mean arterial pressure, and mean left atrial pressure did remain relatively constant (average variation = 2.8 ± 0.6 per cent) during the injection of the microspheres. In addition, the sinus arrhythmia that is present in the awake dogs was eliminated by pacing the heart.

The variation in left ventricular perfusion observed in the sequentially and simultaneously injected animals (Table I) is probably due to chance variation in the gamma counts in the reference arterial blood samples. Extensive experience in our laboratory and elsewhere has demonstrated that gamma counts in the reference samples are rarely identical when duplicate simultaneous samples are obtained from different arteries. Therefore, the actual intra-animal variation in mean left ventricular perfusion was probably much less than the measured values indicate. We minimized these differences in the following ways: (1) left ventricular perfusions which differed from their respective mean perfusion by greater than 25 per cent were deleted; (2) all the data were normalized to eliminate differences in segmental perfusion related to spatial heterogeneity and differences in calculated intra-animal mean left ventricular perfusion. Thus, myocardial perfusion was effectively held constant during the sequential injection of microspheres.

The differences between the average range of segmental perfusion variation in the simultaneously and sequentially injected animals (Fig. 2) suggests that temporal heterogeneity is present in awake dogs studied under basal conditions. The magnitude of the heterogeneity observed is similar to what we have previously reported in studies done in open chest anesthetized dogs.[3]

Recently, Gamble and co-workers[1] reported that venous oxygen saturation measured in small venulae in the myocardium with a microscopic oximetric technique was found to be very heterogenous. They postulated that in adjacent areas in the myocardium there may be heterogeneity of metabolic requirements, coronary flow, or both. This study demonstrates that there is heterogeneity of perfusion, but the mechanism responsible for the temporal and spatial heterogeneity is unclear. Temporal heterogeneity could be related to spontaneous cyclical changes in the tone of small resistance vessels or to time-dependent changes in the metabolic requirements of small myocardial segments coupled to autoregulatory changes in blood flow. Preliminary data reported by Sestier, Mildenberger, and Klassen[2] support the hypothesis that there are spontaneous cyclical changes in the tone of small resistance vessels and that the periodicity of the cycle is between 45 and 90 seconds. If these cyclical changes are asynchronous in small ventricular segments, this could result in the spatial heterogeneity observed in this study.

In summary, this study has demonstrated that spatial and temporal heterogeneity of left ventricular perfusion occurs in awake dogs studied under basal conditions. Whatever the mechanism is of spatial and temporal heterogeneity of perfusion, these phenomena need to be considered whenever flow to small regions of the left ventricular myocardium is being evaluated in reponse to interventions: changes in perfusion to single one gram segments of the left ventricle may be due to temporal or spatial heterogeneity, to the intervention being examined, or to both.

Summary

The purpose of this investigation was to ascertain if spatial and temporal heterogeneity of

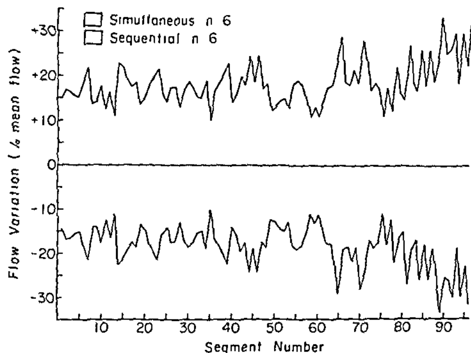


Fig 2 Distribution of segmental flow variations for simultaneous and sequential injections *The middle band indicates the average range of perfusion variability in the simultaneously injected dogs The larger outside band indicates the average range of perfusion for the sequentially injected dogs* All data were normalized to eliminate *the effects of spatial heterogeneity and variance in intra animal mean left ventricular perfusions*

Table II summarizes the spatial heterogeneity observed in this study expressed as the average dispersion of ventricular perfusion The average dispersion was 21 4 ± 1 5 per cent Sphere size did not affect the spatial heterogeneity since the average dispersion observed in dogs studied with either 7 to 10 μ or 15 ± 5 μ microspheres was similar

Temporal heterogeneity The mean left ventricular perfusion for each flow determination in the simultaneously and sequentially injected dogs is shown in Table III In two of the studies (dogs *13* and *22)* only *three batches of labeled* spheres were injected five other flows (10 9 per cent) were deleted because they deviated from their respective intra animal mean perfusions by greater than 25 per cent Although the 25 per cent level was arbitrarily chosen in a previous study[5] in which two reference arterial samples were *withdrawn simultaneously* (this study utilized only one reference sample) in six of 70 pairs of arterial reference samples (8 6 per cent) the gamma counts in the two arterial reference samples differed by more than 25 per cent of their mean Thus the difference in calculated mean left ventricular perfusions shown in this study are *probably* mainly related to chance variations in the gamma counts in the reference arterial blood samples[5, 7]

Average heart rate, mean arterial pressure and left atrial pressure during the three or four injections of microspheres were calculated in the sequentially injected dogs (Group III, Table I) All changes in these measurements were less than 10 per cent of their respective intra animal means and the average *change was 2 8 ± 0 6 per cent*

The average range of perfusion (highest minus the lowest flow in normalized per cent) to each of the 96 segments in the simultaneously and sequentially injected dogs is shown in Fig 2 The data have been normalized to minimize the effects of spatial heterogeneity and intra animal *differences in mean left ventricular* perfusion In *all of the 96 segments* the average range in per cent of segmental flow variations was greater in the sequentially injected dogs than in the simultaneously injected dogs The magnitude of the differences was roughly similar in all groups of ventricular segments The average range in the simultaneously and sequentially injected animals was 16 3 ± 1 7 per cent and 26 0 ± 2 7 per cent respectively ($p < 0.01$)

Discussion

The primary objective of this study was to assess the magnitude of spatial and temporal heterogeneity of perfusion to small segments of the left ventricular *myocardium in awake* dogs studied under basal conditions

The hemodynamics, blood gases and total

Effects of acute hyperkalemia on cardiac excitability

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Study of the effects of elevation of extracellular potassium on electrophysiologic properties of cardiac tissue is of importance to understand changes that take place in acutely ischemic tissue and relate them to disorders of rhythm Harris and colleagues have shown that acute coronary occlusion results in leakage of intracellular potassium into the extracellular space in ischemic tissue These investigators also showed a parallel time course in the potassium loss from ischemic tissue and the incidence of arrhythmias The local accumulation of extracellular potassium was estimated to be as high as 12 mEq /L Elevation of extracellular potassium has several effects on electrophysiologic properties of the myocardium that may contribute to the genesis of these arrhythmias The gradient of intracellular to extracellular potassium lessens when extracellular potassium is elevated and this decreases the resting membrane potential Increased extracellular potassium also increases membrane permeability for potassium lowers membrane resistance and increases repolarizing currents that shorten transmembrane action potential duration *In addition* progressive hyperkalemia has been shown to initially increase conduction velocity and later depress it

Since characteristics of the excitability cycle are also likely to play a role in the genesis of arrhythmias the study reported here was done to determine the changes in threshold for propagated responses throughout the cardiac cycle during progressive elevation of serum potassium The purpose of the study was to define changes in excitability associated with hyperkalemia that might have a role in the occurrence of arrhythmias in the clinical setting rather than to define the effect of steady state hyperkalemia on the strength interval curve Definition of the latter would require both a steady state which is *unlikely to exist in* clinical conditions and determinations of local extracellular potassium and the gradient of extracellular to intracellular potassium which are not possible in the clinical situation

Anodal stimulation was used in this study because this form of stimulation results in a marked lowering of excitability thresholds in the relative refractory period which coincides with the time of the vulnerable period [2]

Methods

Experiments were done on seven mongrel dogs weighing 15 to 32 kilograms anesthetized with alpha chloralose and urethane (50 to 75 c c of a mixture of 4 Gm of alpha chloralose and 60 Gm of urethane in 200 c c of saline) Respiration was maintained by a Harvard volume respirator and body temperature was maintained by a thermal blanket

The chest was opened by a mid sternal incision and the heart was suspended in a pericardial cradle The sinus node was crushed and 2 msec two times diastolic threshold stimuli at 400 msec cycle lengths were delivered simultaneously to bipolar electrodes placed on the right atrium and

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myocardial blood flow occurred in awake dogs under basal conditions Myocardial perfusion was assessed by injecting differently labeled 15 ± 5 μ or 7 to 10 μ microspheres into the left atrium Spatial heterogeneity of perfusion was determined in 24 awake dogs by analyzing the distribution of perfusion to 96 segments of the left ventricle Spatial heterogeneity expressed as the relative dispersion of the segmental perfusion averaged 21 4 ± SE 1 5 per cent The variation in segmental perfusion due to the microsphere technique was assessed by injecting three or four batches of microspheres simultaneously in six of the dogs Temporal heterogeneity was assessed by sequentially injecting three or four batches of microspheres at 1 minute intervals in six other dogs while left atrial pressure arterial pressure heart rate and left ventricular perfusion were held constant The average range of segmental perfusion was greater in the sequentially injected dogs than in the simultaneously injected dogs (26 0 ± SE 2 7 per cent vs 16 3 ± SE 1 7 per cent respectively [$p < 0.01$]) Thus this study indicates that spatial and temporal heterogeneity of left ventricular perfusion is present in awake dogs studied under basal conditions

We are grateful to Dr Judy Kondo for statistical consultation and to Kathy Sheldahl Lynn Cook and Jeanne Coffin for secretarial assistance

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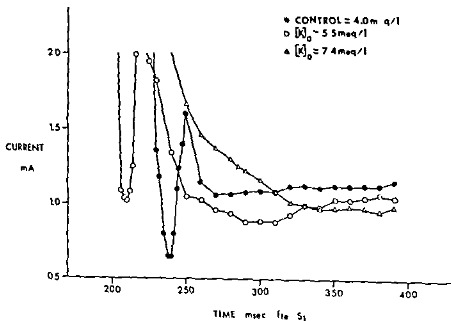


Fig 2 Three superimposed strength intervals are shown from experiment No 4 One control curve is contrasted against two excitability curves done during infusion of potassium (see text for discussion) Serum levels shown during potassium infusion represent average of potassium values at start and completion of excitability curves

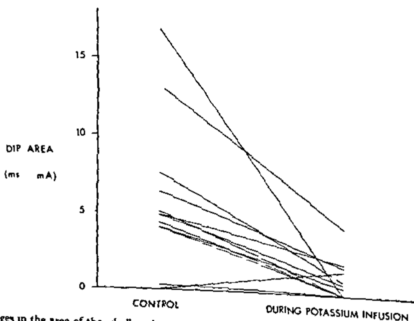


Fig 3 Changes in the area of the "dip" in the anodal strength interval curve are shown for the average of two control dip areas contrasted with the dip area during infusion of potassium.

Characteristics of anodal excitability curves and the features measured in this study are diagramatically illustrated in Fig 1 End diastolic threshold was taken as the average of three determinations measured at 10 msec increments during end diastole The supernormal period of excitability was defined as the time in the cardiac cycle following the relative refractory period when threshold was below end diastolic threshold The relative refractory period corresponded to that portion of the excitability curve where there was a rapid rise in threshold values with slight increases in prematurity of test stimuli The dip was that portion of the relative refrac

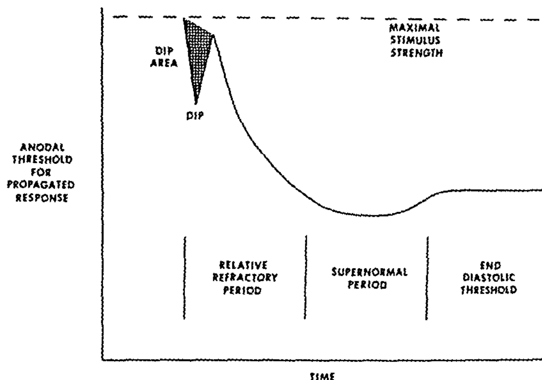


Fig 1 The form of the excitability curve The excitability curve shows stable end diastolic thresholds on the right With increasing prematurity of the stimuli the thresholds show a supernormal period of excitability and then a relative refractory period In the relative refractory period there is an abrupt lowering of the threshold values called the "dip The area of the dip *represented by the cross hatched area* was measured by planimetry

anterior surface of the ventricles The basic drive was delivered to the ventricle so that changes in AV conduction during potassium infusion did not affect timing features of the excitability curve and the atrium was driven simultaneously to avoid retrograde conduction and atrial conducted complexes The anodal test stimuli were delivered to a 3 mm gold plated unipolar electrode sutured to either the epicardial surface of the anterior right or left ventricle A gold plated cylinder 7 mm long by 2 mm diameter was placed in the subcutaneous tissue of the right leg to serve as a remote cathode Constant current anodal stimuli were generated from a specially constructed stimulator, with digitally controlled output and a resolution of 1 microampere Anodal constant current test stimuli were of 2 msec duration and delivered after every third basic drive cycle The intensity of stimulation was increased by 10 microampere increments until a 50 per cent incidence of propagated responses was observed in a vertical lead ECG which was monitored on an oscilloscope or a maximal strength of 2 mA was reached Stimuli greater than 2 mA were not used to avoid tissue injury at the test site The anodal test stimuli were given at 10 msec intervals from end diastole to the relative refractory period and to avoid missing the dip portion of the excitability curve the test stimuli were delivered at 1 to 2 msec increments in earlier portions of the cycle By giving test stimuli after every third cycle it was possible to plot one entire excitability curve in 20 minutes or less

Prior to measurement of excitability curves, 20 to 30 minutes were allowed for ST displacement due to surface injury from the ventricular test electrodes to dissipate After two control excitability curves were determined and control serum potassium was drawn potassium infusion was started and maintained at a constant rate in each dog experiment Several excitability curves were determined in each animal while serum potassium increased during potassium infusion given at a constant rate Potassium chloride in a volume of 200 to 500 c c of saline was infused by the external jugular vein at rates from 0 67 to 6 0 mg /Kg /min by a Harvard infusion pump Potassium excitability curve determinations were started only after 20 minutes of infusion time Serum samples for potassium were drawn at the right femoral vein at the start and completion of each strength interval curve during the potassium infusion Potassium infusion was terminated if an interventricular conduction defect was observed on the monitored ECG lead so the effects of changes in time of activation at the test site on the form and timing of the strength interval curves were minimized

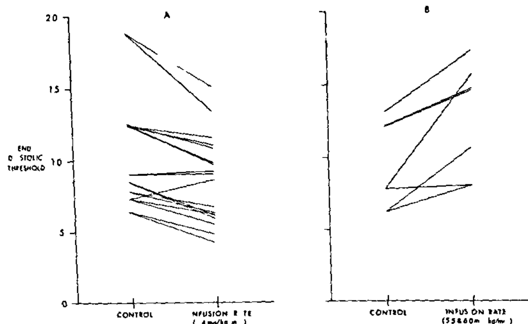


Fig 5 A and B Comparison of the effect of two groups of infusion rates is shown to have opposite effects on end diastolic threshold Infusion rates of less than or equal to 4 mg /Kg /min were associated with lower end-diastolic thresholds than controls *(graph A)* while infusion rates of 5 5 and 6 0 mg /Kg /min. were found to cause elevation of end-diastolic thresholds

lessening of dip excitability persisted through out the period of observation in these experiments even if potassium infusion was terminated

Changes in end diastolic excitability The changes in end diastolic excitability during potassium infusion were complex As illustrated in Fig 4A small elevations of serum potassium that averaged 1 7 mEq /L but did not elevate serum potassium to greater than 6 mEq /L were associated with lowered end diastolic thresholds that averaged 18 per cent below controls ($p < 005$) As seen in Fig 4B further elevation of serum potassium above 6 mEq /L had unpredictable effects on end diastolic excitability However as seen in Fig 5 both high and low infusion rates of potassium were correlated with changes in end diastolic threshold although the effects at high and low rates were opposite Infusions of potassium of 4 mg /Kg /min or less lowered end diastolic thresholds by an average of 21 per cent compared to controls ($p < 015$) Higher infusion rates of 5 5 and 6 0 mg /Kg /min elevated end diastolic thresholds by an average of 37 per cent compared to controls ($p < 025$)

Other changes in excitability curves with extracellular hyperkalemia Supernormal periods of excitability were seen in only 29 per cent of control excitability curves and were of variable durations and threshold levels When present in controls they tended to be abolished during potassium infusion and were found in only 16 per cent of excitability curves during potassium infusion In 70 per cent of cases both the dips' and the relatively refractory period of excitability curves determined during potassium infusion shifted position in the cardiac cycle by more than 10 msec (see Table I) These portions of the curves compared to control curves shifted earlier in the cardiac cycle in 35 per cent and later in 35 per cent with no correlation with serum level or rate of infusion Potassium infusion also changed the slope of the excitability curve during the relative refractory period With serum levels of 7 mEq /L or greater the slope of the threshold values during the relative refractory period was decreased in 86 per cent of the excitability curves so the slope during the relative refractory period was inversely related to the serum concentration of potassium

Discussion

Use of the anodal excitability curve and accurate measurement of the dip phenomenon allow assessment of excitability changes that occur during the vulnerable period as well as end diastolic excitability With infusions of potassium

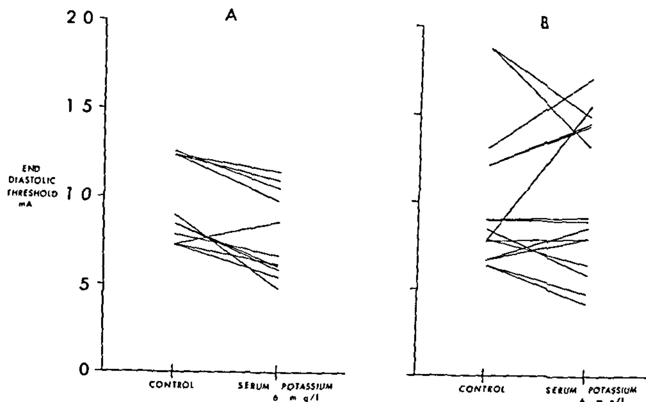


Fig 4 A and B Effects of serum elevations of potassium on changes in end-diastolic threshold are shown for elevations up to 6 mEq /L of potassium in graph A This is contrasted with serum elevations of greater than 6 mEq /L in graph B Elevations of serum potassium up to 6 mEq /L were associated with increased end diastolic excitability while further elevations of serum potassium did not correlate with a predictable change in end diastolic excitability

tory period where there was a lowered threshold despite increased prematurity of the stimuli The 'dip was measured in width depth and temporal location The dip in addition, was characterized by measurement of its area The open end of the dip was closed off from the highest point in the relative refractory period at the temporal end of the dip' to a point at the beginning of the dip' at the maximal threshold determined in this study and the enclosed area was measured with a planimeter

Results

Form of excitability curves The form of three excitability curves superimposed in Fig 2 show the results from experiment No 4 in Table I The control excitability curve shows a period with uniform end diastolic thresholds Earlier in the cardiac cycle there is a slight lowering of excita bility thresholds below end diastolic values that is compatible with the supernormal period of excitability Still earlier there is a rise in threshold values corresponding to the relative refractory period Earlier yet in the cardiac cycle there is an unusually large dip in threshold values It can be seen that the maximal anodal excitability occurs at quite a premature interval The two curves determined during potassium infusion have lower end diastolic thresholds than the control curve and the dip is diminished in one curve and abolished in the other

The major characteristics of excitability curves determined during 28 control periods and 31 excitability curves during infusions of potassium are shown in Table I, and are described below

Changes in excitability during the dip The changes in excitability during the 'dip which corresponds to the excitability during the vulnerable period are shown in Table I and Fig 3 The area of the dip was diminished from control dip areas with all infusion rates of potassium used in this study, $p < 001$ In 61 per cent of the excitability curves the dip was eliminated entirely The depth, width and area were diminished in the remaining excitability curves with the exception of one test site in dog No 7 where there was no dip in the control excitability curves and a very small dip was present during potassium infusion The diminu tion of the size of the dip occurred within the first 20 minutes of potassium infusion before threshold measurements were taken and the

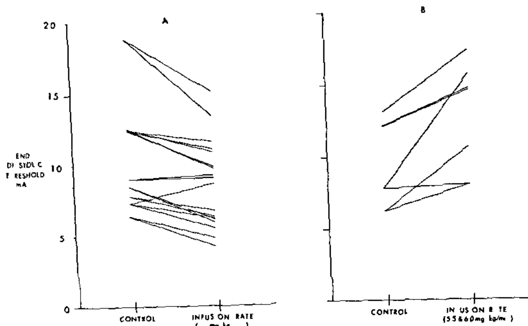


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Discussion

Use of the anodal excitability curve and accurate measurement of the dip phenomenon allow assessment of excitability changes that occur during the vulnerable period as well as end diastolic excitability With infusions of potassium

Table I Data from strength interval curves from 14 epicardial sites before and during potassium infusion

Dog	Electrode site	End diastolic threshold mA C*		End diastolic threshold mA ↑[K]o	Onset of RRP msec from S C	Onset of RRP msec from S ↑[K]o	Time of max dip msec from S1 C	Time of max dip msec from S1 ↑[K]	Area of dip (mA msec) C		Area of dip (mA msec) ↑[K]	Averaged serum potassium level mEq/l C	Averaged serum potassium level mEq/l ↑[K]	Rate of potassium infusion mg/Kg/min
1	A	>2	>2 0 (mean)		—*		194		7 0	5 3 (mean)		2 8		0
		>2			—		196		3 5					0
				1 88		—		—			0		3 5	0 67
				>2		—		—			0		5 0	0 67
	B	0 70	73 (mean)		260		220		4 6	5 1 (mean)		2 8		0
		0 76			260		226		5 6					0
				0 86		270		0			0		4 1	0 67
				0 62		270		0			0		3 5	0 67
				0 55		270		0			0		3 7	0 67
2	A	1 26	1 31 (mean)		230		182		0 4	3 (mean)		4 9		0
		1 36			220		178		0 2					0
				>2 0		—		0			0		6 5	5 5
				1 72		—		0			0		7 7	stopped
	B	0 80	78 (mean)		190		0		0			4 9		0
		0 76			190		0		0					0
				0 80		185		0			0		7 8	5 5
				1 56		—		0			0		7 3	stopped
3	A	0 88	90 (mean)		200		166		4 9	4 9 (mean)		3 6		0
		0 92			200		168		4 9					0
				0 90		210		143			1 4		6 6	4 0
				0 92		240		0			0		8 1	4 0
	B	0 69	64 (mean)		260		218		4 9	4 0 (mean)		3 6		0
		0 58			290		228		3 2					0
				0 48		240		0			0		5 7	4 0
				0 42		250		0			0		7 5	4 0
4	A	>2 0	>2 0 (mean)		—		192		5 5	4 9 (mean)		4 0		0
		>2 0			—		200		4 2					0
				1 68		—		174			2 0		6 3	4 0
				1 79		—		190			1 9		7 5	stopped
	B	1 13	1 26 (mean)		260		240		15 6	13 1 (mean)		4 0		0
		1 38			260		230		10 8					0
				1 05		250		210			8 5		5 5	4 0
				0 97		280		0			0		7 4	stopped

C = control state ↑[K] = measurements during potassium infusion — indicates incidences where data were not available from the excitability curve

of ≤ 4 mg/Kg/min end diastolic excitability increased while infusion rates > 4 mg/Kg/min caused depression of end diastolic excitability Serum levels of potassium were only helpful in predicting changes of end diastolic excitability in this study if the serum elevation did not exceed 6 mEq/L With these small elevations of serum potassium there was increased end diastolic excitability

Evaluation of the literature on the effect of potassium on end diastolic excitability is complex because of the various preparations and various modes of potassium administration Studies on isolated cardiac tissue with changes in extracellular potassium have shown an increased excitability with moderate increases in extracellular potassium and a decrease in excitability with further elevations of extracellular potassium [13,17] Domingues and Fozzard[13] showed that elevations of potassium from 2 7 to 4 0 mM were associated with the resting membrane potential approaching the threshold potential and they considered this responsible for the enhanced excitability found With higher levels of extracellular potassium there was a slight increase in threshold potential needed for stimulation They postulated this was

Table I continued

Dog	Electrode site	End diastolic threshold mA C	End diastolic threshold mA +[K]	Onset of RRP msec from S C	Onset of RRP msec from S +[K]	Time of max dip msec from S C	Time of max dip msec from S +[K]	Area of dip (mA msec) C	Area of dip (mA msec) +[K]	Averaged serum potassium level mEq/l C	Averaged serum potassium level mEq/l +[K]	Rate of potassium infusion mg/Kg/min
5	A	063 $\overline{67}$		245		214		93 $\overline{76}$		38		0
		0 0		250		216		59				0
			080		240		0		0		63	60
			106		270		196		18		63	stopped
	B	103 $\overline{121}$		230		210		164 $\overline{169}$		38		0
		138		230		208		173				0
			146		—		0		0		66	stopped
			145		—		0		0		67	stopped
6	A	188 $\overline{188}$		—		198		64 $\overline{41}$		34		0
		187		—		194		18				0
			150		230				10		63	40
			133		230		0		0		73	40
	B	076 $\overline{79}$		240		210		32 $\overline{44}$		34		0
		08		240		210		56				0
			06		215		0		0		52	40
			063		220		0		0		69	40
7	A	0 4 $\overline{85}$		260		230		130 $\overline{69}$		32		0
		096		260		228		08				0
			061		220		184		3.2		49	2.0
			059		260		202		22		58	20
			059		260		0		0		61	20
	B	123 $\overline{124}$		260		—		0		32		0
		124		260		—		0				0
			115		260		205		2.2		44	2.0
			110		260		198		2.4		51	20
			098		260		0		0		60	2.0

secondary to partial inactivation of the sodium inward current resulting from depolarization of the tissue

Results from in vivo animal studies on whether slight increases in extracellular potassium increase or decrease excitability are divided All agree that high levels of potassium are associated with depression of excitability Siebens and associates were the first to show that there was an increased excitability during potassium administration that was later followed by depression of excitability Han and colleagues and Lee and coworkers reported similar findings Surawicz and associates[10] and Ettinger and colleagues found only a depression of excitability during potassium infusion Logic and Elharrat and co workers found with local perfusion of a coronary artery with potassium solutions that there was also an early increase in excitability followed by depression of excitability Ettinger and associates using a similar preparation but different infusion rates found only a depression of excitability Studies done in man show a similar conflict as to whether potassium caused an increase in excitability Surawicz and associates reported on two patients one with renal failure and hyperkalemia and the other who was receiving potassium infusions Both patients had depression of excitability to pacing In studies on five patients Gettes and colleagues measured excitability at several points in the cardiac cycle during progressively more concentrated infusions of potassium and found only depression of excitability In contrast to these reports Walker and co workers[2] found that two patients who failed to respond to artificial pacing could be driven following potassium administration Preston and colleagues studied the effects of several potassium glucose and insulin solutions on threshold for pacing in patients Potassium chloride infusions lowered

end diastolic thresholds but with potassium solutions containing mixtures of glucose and insulin, thought to promote increases of potassium intracellularly higher end diastolic thresholds were found

In contrast with those authors who found a transitory increase in excitability with potassium elevation our results show that this increased end diastolic excitability *may persist for a period* of greater than several hours rather than only a few minutes In this study the most consistent effect of hyperkalemia on cardiac excitability was its effect on vulnerable period excitability At all infusion rates of potassium used, 'dip threshold was increased Area of dip ' and width of the dip in the excitability curve were also diminished The relationship of the dip of the anodal excitability curve to the pathogenesis of arrhythmias is not well established However the dip of the excitability curve coincides with the vulnerable period for arrhythmias [11, 12] The form of the dip of the excitability curve has been found to be a predictor of the type of arrhythmia produced by a train of low intensity stimuli Elevation of threshold during the dip has been shown to occur with quinidine and procainamide ' Owens and Gamble[13] have recently shown that elevation of thresholds by potassium during the dip is associated with a decrease in vulnerability to accelerated arrhythmias In view of *these relationships of vulnerable period and* initiation of arrhythmias one might speculate that the local hyperkalemia associated with acute infarction may be deleterious in its effects in shortening refractory periods and slowing conduction, thus favoring reentrant arrhythmias However the effect of local hyperkalemia on vulnerable period excitability may be protective by inhibition of very premature ectopic depolarizations

Summary

The effect of hyperkalemia on the form of anodal excitability curves was determined in seven dogs to better understand its role in the genesis of arrhythmias in ischemic tissue Threshold for excitation was determined with 2 msec stimuli at 10 msec intervals in late and 2 msec intervals in early portions of the cardiac cycle during control periods and during potassium infusion Stimulus intensity was increased at 10 μamp increments Infusion of potassium at *4 mg /Kg /* min or less lowered end diastolic threshold in 18 of 20 cases by an average of 21 per cent ($p < 01$5) Potassium infusion at 5 5 to 6 mg /Kg /min however, raised end diastolic threshold in seven of eight cases, by an *average of 37 per cent* ($p < 025$) Serum potassium was not an accurate predictor of potassium effect *on end diastolic* threshold In 27 of 29 determinations threshold of the 'dip' of the strength interval curve and thus threshold during the vulnerable period were raised during potassium infusions at all rates studied

In conclusion, low dose potassium infusion lowered threshold late in the cardiac cycle and increased the threshold early in the cardiac cycle *High dose potassium infusion raised threshold* throughout the cardiac cycle While local hyperkalemia in ischemic tissue is known to have several deleterious effects these findings suggest that its modification of excitability may be protective

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Effect of lidocaine on the atrial fibrillation threshold

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The antiarrhythmic action of lidocaine has been well demonstrated in experimental and clinical studies Because of its effectiveness and low toxicity it has become the drug of choice in the initial treatment of ventricular tachyarrhythmias [1-7] It is generally considered ineffective in the treatment of supraventricular arrhythmias and it is usually not mentioned as an agent worth trying in refractory atrial tachyarrhythmias [5, 8-10] However in some instances, lidocaine is effective in treatment of atrial tachyarrhythmias [4, 11-14] Lidocaine produces similar electrophysiologic effects on atrial and ventricular action potential although higher concentrations are required in the atrium,[15-19] and it elevates the ventricular fibrillation threshold (VFT) [20-31] The purpose of this investigation is to study the effect of lidocaine on the atrial fibrillation threshold (AFT)

Material and methods

Mongrel dogs weighing 25 to 50 pounds were anesthetized with 25 mg of sodium pentobarbital per kilogram of body weight intravenously Respiration with room air was maintained by means of a Harvard ventilatory pump and an endotracheal tube Tidal volume and respiratory rate were set according to the weight of the animal The blood pressure was measured via a No 7 French catheter introduced in the descending aorta through a femoral artery The electrocardiogram was monitored through an oscilloscope and was recorded each time the atrial fibrillation threshold was measured The atrial fibrillation threshold was measured with a method similar to that used for the determination of the ventricular fibrillation threshold [24] Electrical impulses, programmed by an American Electronics stimulator were delivered to the atrial myocardium via specifically constructed bipolar epicardial electrodes attached to the right atrium The electrodes consisted of two stainless steel wires, 1 mm in diameter, embedded 10 mm apart in a small acrylic plate At every tenth heart beat the system delivered a series of rectangular pulses of 2 5 msec duration each at intervals of 10 msec The series of impulses started immediately after the onset of the P wave and ended at the end of the QRS adequately covering the atrial vulnerable period Every 30 beats the stimulus amplitude was increased at increments of one mA until atrial fibrillation was observed (Fig 1) Spontaneous reversion to sinus rhythm was allowed to occur The current delivered to the dog was measured with a current probe amplifier and was displayed on a storage oscilloscope Each determination of atrial fibrillation threshold was done twice The results of these two measurements were either identical or different by no more than one mA The first value obtained was used for the statistical analysis Statistical analysis of the second values or the average of the two values yielded practically identical results During the experiments the heart rate was kept constant at

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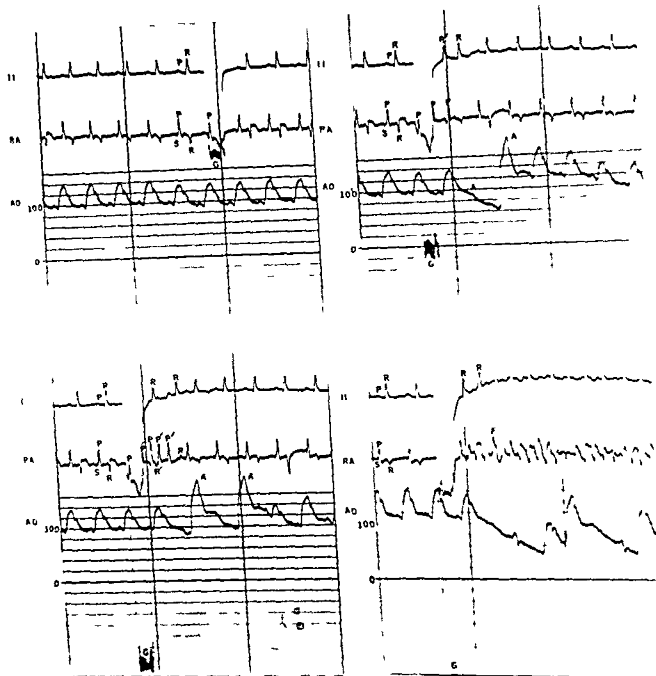


Fig. 1. Determination of atrial fibrillation threshold. *II* ECG Lead II. *RA* right atrial electrogram. *AO* aortic pressure in mm Hg. *S* pacemaker stimulus. *Left upper panel* A gaited series of impulses approximately 3 mA. *(G)* is delivered directly on the right atrium but has no effect on the atrial activity. *Right upper panel* The amplitude of the gaited impulses *(G)* is higher (7 mA.) causing an interpolated premature atrial contraction *(p)* resulting in premature ventricular activation *(R)*. *Left lower panel* Further increase in the amplitude of the stimulus (10 mA.) causes repetitive atrial contractions *(P')*. *Right lower panel* Further increase in the amplitude of the stimulus (15 mA.) results in atrial fibrillation *(F)*.

25 beats per minute above the spontaneous rate by atrial pacing utilizing a Grass stimulator and another pair of epicardial electrodes attached to the right atrium. The atrial fibrillation threshold was measured every five minutes for 15 minutes before, one minute after, and for 25 minutes after the administration of 3 mg./Kg. lidocaine intravenously in two minutes (1 per cent solution). This dose was selected since inconsistent effects with smaller doses of lidocaine (1 and 2 mg./Kg.) were

Table I Effect of lidocaine (3 mg /Kg) on the atrial fibrillation threshold (mA)

Time (min)	n	Mean	Std error	t	P
		Lidocaine			
Control	10	14 00			
1	10	41 40	3 177	−8 624	< 0 001
5	10	29 30	1 868	−8 190	< 0 001
10	10	23 90	1 636	−6 051	< 0 001
15	10	18 80	0 964	−4 980	< 0 001
20	10	15 50	0 428	−3 503	< 0 005
25	10	14 60	0 454	−1 327	NS
		Control			
Control	5	15 60			
1	5	15 60	0 4447	0 000	NS
5	5	14 80	0 510	0 784	NS
10	5	15 60	0 548	0 000	NS
15	5	15 80	0 583	−0 343	NS
20	5	16 20	0 678	−0 885	NS
25	5	15 60	0 316	0 000	NS

NS = not significant by paired comparison

Table II Effect of lidocaine (2 mg /kg IV) on the ventricular fibrillation threshold (mA)

Time (min)	n	Mean	Std error	t	P
		Lidocaine			
Control	10	11 00			
1	10	33 30	6 178	−3 610	0 005
5	10	20 80	1 685	−5 815	0 001
10	10	17 00	2.082	−2 882	0 010
15	10	14 40	1.522	−2.234	0 050
20	10	14 30	1 892	−1 744	NS*
25	10	13 60	1 809	−1 438	NS
		Control			
Control	10	9 50			
1	10	9 90	0 476	−0 840	NS
5	10	9 40	0 433	0 231	NS
10	10	9 40	0 379	0 264	NS
15	10	9 50	0 471	0 000	NS
20	10	9 70	0.512	−0 391	NS
25	10	9 70	0 359	−0 557	NS

NS = not significant by paired comparison

noted Control experiments were performed in five animals (injection of 0 3 ml /Kg of normal saline in two minutes)

In a different set of ten animals, the ventricular fibrillation threshold (VFT) was measured by delivering a gated series of impulses to the right ventricular myocardium via a similar pair of epicardial electrodes The heart rate was kept constant by atrial pacing at 25 beats above the spontaneous sinus rate The series of impulses started immediately after the R wave and was adjusted individually to end after the peak of the T wave, thus covering the ventricular vulnerable period Every thirty beats the current was increased at increments of 1 mA until ventricular fibrillation was observed Defibrillation was performed by delivering DC shocks (approximately 200 Watt sec) across the chest The VFT was measured every five minutes for fifteen minutes before, one minute after and for 25 minutes after the intravenous administration of lidocaine (2 mg /Kg) Ten control experiments were also performed

Results

The technique utilized allowed us to measure the AFT and VFT in a reliable fashion Each measurement was duplicated and there was no consistent change in either AFT or VFT in the control experiments (Tables I and II and Figs 2 and 3) There were no significant changes in blood pressure (maximum change less than 5 mm Hg) and the heart rate was kept constant by atrial pacing The serum potassium concentration was 4 28 ± 1 36 mEq/L

A marked increase in the AFT was noted after intravenous injection of lidocaine (3 mg /Kg) in all animals This increase was statistically significant ($P < 0\ 001$) and lasted more than 15 minutes (Table I and Fig 2) Injection of 2 mg /Kg of lidocaine intravenously in 2 minutes did not change the AFT in a consistent fashion However in a separate set of experiments lidocaine (2 mg /Kg) produced an increase of the ventricular fibrillation threshold (Table II and Fig 3) This increase was similar in magnitude to the increase of AFT produced by 3 mg /Kg of lidocaine intravenously

Discussion

The increase of ventricular fibrillation threshold after intravenous administration of lidocaine (2 mg /Kg) is similar to that reported by Gerstenblith and associates[20] and by Borer and asso

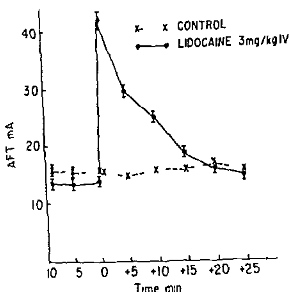


Fig 2 Effect of lidocaine (3 mg/Kg IV) on the atrial fibrillation threshold.

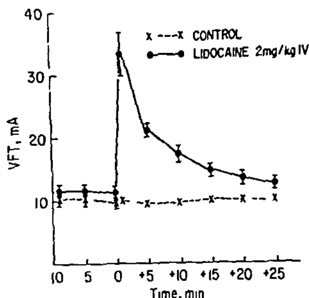


Fig 3 Effect of lidocaine (2 mg/Kg IV) on the ventricular fibrillation threshold

ciates and consistent with the known effectiveness of lidocaine in the treatment of ventricular tachyarrhythmias An increase of the atrial fibrillation threshold was also found in this study This increase was of similar magnitude and exhibited a similar time course to the change of ventricular fibrillation threshold but was observed after injection of higher dose of the drug (3 mg/Kg) A lower dose (2 mg/Kg) did not have a consistent effect on the AFT producing a transient increase in some animals and no effect in others This lower sensitivity of the atrial tissue to lidocaine has been reported in electrophysiological studies Mandel and Bigger[4] reported decreases in the amplitude and rate of rise of action potential and prolongation of the effective refractory period of atrial fibers only after perfusion with high concentrations of lidocaine Similarly Kabela[25] found that lidocaine (2 mg/ml) enhance the efflux of ^{42}K from ventricular stips and Purkinje fibers but did not accelerate K efflux from atrial stips However higher concentrations were not tried[2] Singh and Vaughn Williams[5] showed a decrease in automaticity maximal driving frequency contraction and maximum rate of depolarization of rabbit atria These effects were evident at lower concentrations of lidocaine when the nourishing solution contained 5 6 mM KCl than when it contained 3mM KCl The mean serum potassium concentration in our experiment was 4 28 ± 1 36 mEq/L

The elevation of AFT reported here and the data reviewed above suggest that lidocaine possesses an antiarrhythmic effect on the atria although higher than usual doses may be required This opinion is further supported by the admittedly not common success of lidocaine in suppressing atrial arrhythmias in the clinical setting[1, 2, 4] We did not obtain lidocaine blood levels and the dose that we found consistently effective raising the AFT is higher than the dose commonly used in humans corresponding to approximately 200 mg for the average adult However since lidocaine possesses very low serious toxicity such doses are given in certain instances[2, 5, 6-9]

Summary

The effect of lidocaine on the atrial fibrillation threshold (AFT) and the ventricular fibrillation threshold (VFT) was studied in anesthetized dogs In ten animals injection of lidocaine 2 mg./Kg intravenously resulted in a marked increase of the ventricular fibrillation threshold (from 11 0 ± 1 5 to 33 3 ± 6 2 mA $P < 0.001$) In another group of ten animals lidocaine did not have consistent effect on the atrial fibrillation threshold However a dose of lidocaine of 3 mg/Kg intravenously produced a significant increase in AFT (from 14 0 ± 0 56 to 41 1 ± 0 32 mA $P < 0.001$) No changes in AFT or VFT were noted in control experiments The data suggest

that lidocaine possesses an antiarrhythmic effect on the atria but higher than usual doses are required

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Mid ventricular hypertrophy without clinically apparent obstruction

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A left ventricular outflow tract gradient is seen in a majority of patients with asymmetric septal hypertrophy and now has recently been described in mid ventricular obstruction The level of septal hypertrophy in this entity is somewhat lower than that in classical idiopathic hypertrophic subaortic stenosis (IHSS) but the clinical features as reported by Falicov and colleagues seem similar to those of classical IHSS Our patient with obvious mid ventricular obstruction at autopsy had no clinically apparent features of outflow tract obstruction Although the lack of correlation between the degree of obstruction and clinical features is known this case points up the lack of reliability of the Valsalva maneuver in assessing obstruction when hypertrophy is at the mid ventricular level

Case Report

A 13-year-old boy presented for evaluation with a two year history of slight *exertional* dyspnea He had never been cyanosed did not suffer from squats had never complained of palpitation syncope chest pain nor of symptoms of left heart failure There was no family history of *cardiovascular disease* of any kind and he had not had any illnesses other than the usual childhood infections On examination his blood pressure was 130/60 his pulse was of normal amplitude without an abnormally brisk upstroke or a bifid quality The cardiac impulse was in the fifth intercostal space and was normal in amplitude without a double impulse There was no clinical evidence of enlargement of either ventricle No fourth or third sound was heard and the only murmur audible was a Grade 2/6 soft, ejection systolic murmur best heard at the left sternal border with radiation to the carotids An apical murmur was not present The Valsalva maneuver performed on several occasions resulted in complete disappearance *of the* murmur A tentative diagnosis of asymmetric septal hypertrophy was entertained because of the electrocardiographic *pattern of deep septal* Q waves in the left precordial leads (Fig 1) We did not feel that obstruction was present because of the murmur's response to changes in *preload* and afterload induced by the Valsalva maneuver

No further investigation was carried out as the dyspnea disappeared spontaneously over several months and *did not* recur Propranolol was not prescribed both because of the lack of clinically apparent obstructive features and the lack of symptoms Sixteen *months* later the boy collapsed and was brought to the Emergency Department where resuscitation was unsuccessful. Autopsy revealed a heart which was moderately enlarged and weighed 400 g The left ventricle was irregularly hypertrophied with the hypertrophy being maximal in the anterior half of *the interventricular* septum and the anterior wall of the left ventricle (Figs 2 and 3) The septal wall bulged into the *left* ventricular chamber at a level 4 cm below the aortic valve much lower than is usually seen in IHSS There was *no* endocardial thickening or mural thrombus in this area of hypertrophy The measurements of left ventricular wall thickness were as follows

Mid septum (anterior)	24 mm
Anterior wall	22 mm
Lateral wall	18 mm
Posterior wall	16 mm
Mid septum (posterior)	1? mm

Fibrosis and scarring were seen *in the* areas of maximal hypertrophy but no fibrosis was *seen in* the posterior wall or the posterior interventricular septum The coronary arteries were normal in size and distribution *No* plaques were present Histological examination showed *the* classic features of IHSS with an irregularity of muscle pattern excessive branching and whorling of muscle fibers (*Fig 4*) variation in size and staining of muscle fibers and nuclei, and marked interstitial fibrosis. In some areas the fibrosis showed a fir tree like

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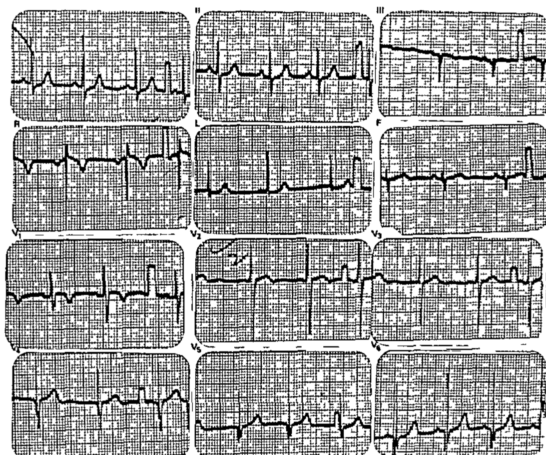


Fig 1 Twelve lead ECG showing pattern of deep septal Q waves in the left precordial leads



Fig 2 Photograph of the anterior part of the left ventricle showing irregular hypertrophy which is greatest in the anterior half of the interventricular septum and the anterior wall at midventricular level (well below the aortic valve)



Fig 3 Horizontal section of left ventricle at midventricular level showing septal encroachment



Fig 4 Histologic section of left ventricle showing excessive branching and whorling of muscle fibers and irregularity of muscle pattern classic features of IHSS

pattern (Fig 5) Examination of the conduction system showed intimal thickening of the AV nodal artery but no degenerative changes in the sinus node AV node or bundle of His.

Discussion

Although our patient did not undergo hemodynamic or angiographic investigation we felt reasonably confident that there was no significant obstruction on the basis of the lack of intensification of the murmur during the Valsalva maneuver In fact the murmur disappeared completely No third or fourth sound and the lack of mitral regurgitation seemed to augur against the diagnosis of asymmetric septal hypertrophy which was clearly suspect because of the electrocardiogram The autopsy clearly reveals the mid ventricular hypertrophied zone which was undoubtedly responsible for enough turbulence to generate the murmur In contrast to the two patients in Falicov s article who had both clinical and hemodynamic evidence of obstruction our



Fig 5 Fir tree pattern of certain fibrosed areas is clearly shown in this enlarged section of the left ventricle

patient seemed not to have this feature of asym metric septal hypertrophy Since our own case had no apparent symptoms once the dyspnea disappeared, no drugs and of course no surgery were considered We agree with Spodick s description of IHSS as a disease of pitfalls and para doxes and would suggest that propranolol be used in patients with mid ventricular obstruction even in the absence of clinical features in the hope of reducing the incidence of sudden death While the Valsalva maneuver may be effective for bringing out clinical features of obstruction when the hypertrophy is subvalvar, we feel that this test may be invalid when hypertrophy is at a lower level

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Termination of ventricular tachycardia by a chest thump over the area of paradoxical pulsation

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Methods for the termination of ventricular tachyarrhythmias include electrical conversion[1] intravenous administration of antiarrhythmic agents such as lidocaine[2] or procainamide[3] or a direct blow to the chest wall

The relative efficacy of all these methods is variable and there are instances of failure with all. Chest thump has been reported to be effective in patients with acute myocardial infarction[4] having ventricular tachycardia We have found that in patients with ventricular aneurysm an indiscriminated thump to the precordium is usually ineffective When the blow is directed to the area of maximal paradoxical pulsation we have been able to convert 3 episodes in two patients We report in this communication these experiences

Case presentation

Case 1 A 44 year-old male known diabetic controlled with insulin was in fairly good health until one year prior to admission when he was told that he had an enlarged heart and adult onset diabetes mellitus At that time he was found to be in congestive heart failure and had severe angina The patient was placed on Digoxin and furosemide and did well. Two months prior to admission the patient developed increasing angina, shortness of breath dyspnea on exertion and pain relieved by nitroglycerin One month prior to admission the patient developed precordial chest pain which lasted 3 to 10 minutes followed by two similar episodes through the night The following day he developed chest pain with nausea and vomiting shortness of breath and palpitations, not relieved by nitroglycerin This pain lasted 3 hours and the patient was admitted to another hospital and told he had an anterior wall myocardial infarction substantiated by ECG and enzymes The patient improved and was doing fairly well until ten days later when he had cardiac arrest with ventricular fibrillation Post resuscitation the patient developed right lower lobe pneumonia probably secondary to aspiration. This was treated with improvement The patient also had an 8-hour episode of hypotension post arrest which was treated with fluids and dopamine with improvement Three days later the patient again had cardiac arrest and had ventricular fibrillation post arrest he had frequent PVC s and was treated with procainamide HCl and quinidine On the day prior to the day of transfer to our hospital the patient had frequent runs of ventricular tachycardia with hypotension abolished by intravenous propranolol The patient was admitted to our hospital for further evaluation and management

Physical examination On admission the patient was afebrile the pulse was 114 slightly irregular the blood pressure was 100/80 and the respiratory rate was 40 Examination of head eyes ears nose and throat was within normal limits. The chest exhibited diffuse coarse rhonchi Dullness and decreased breath sounds were evident at the right base There were bibasilar rales. Cardiovascular exam showed relieved S3 and S4 sounds with no murmur The point of maximal impulse was 1 to 2 cm left of the mid clavicular line Examination showed the abdomen to be benign Neurologic features were grossly intact External examination revealed pulses full, and no cyanosis edema or clubbing

Laboratory data Chest x ray revealed cardiomegaly with right pleural effusion. Data base included SMA 6 chlorid 91 Co 22, potassium 6 sodium 1?6, BUN 28 glucose 3 5 creatinine 1 6 hemoglobin and hematocrit 13 5 and 4? 7 WBC 13,100 Prothrombin time was 14 1 with 10 5 with partial thromboplastin time 38 Urine was essentially normal Blood gas revealed pH 7.52 Pco 22, Po and bicarbonate 18

The impression was atherosclerotic heart disease with

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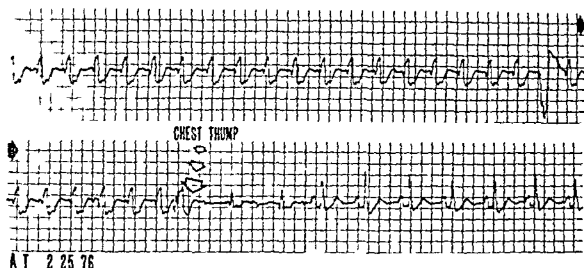


Fig 1 Continuous Lead II of the electrocardiogram shows ventricular tachycardia with one extrasystole at the end of first stop Chest thump was delivered to the area of paradoxical pulsation This allows a supraventricular beat to appear followed by a second similar beat and then by sinus rhythm

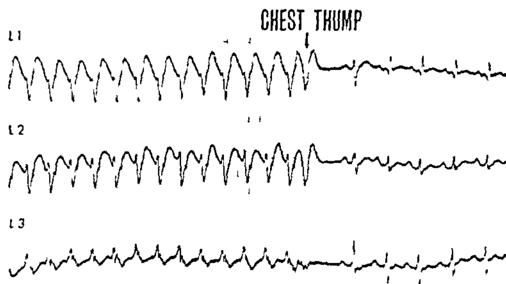


Fig 2 Simultaneous Leads I II and III of the electrocardiogram showing ventricular tachycardia A chest thump was delivered to the area of aneurysmal pulsation Quickly an extrasystole appeared followed by resumption of normal sinus rhythm

recent anterior wall myocardial infarction recurrent ventricular tachycardia and early anterior left ventricular aneurysm

Upon admission to the Coronary Care Unit he was found to have ventricular tachycardia at a rate of 120 beats per minute (Fig 1) A chest thump over the area of paradoxical pulsation converted the rhythm to sinus Patient was then started on a combination of procainamide 500 mg every four hours and quinidine sulphate 300 mg every six hours Two months later he underwent cardiac catheterization and left ventricular and coronary angiography An anteroapical left ventricular aneurysm was found and successfully removed surgically The *patient* has done well after surgery on daily digoxin and procainamide 500 mg every six hours.

Case 2 A F a 78 year old man was admitted to the hospital with a chief complaint of epigastric pain unrelieved by nitroglycerin He denied palpitations diaphoresis dizziness, nausea and shortness of breath There was a history of previous anterior wall myocardial infarction The electrocardiogram taken in the emergency room revealed ventricular tachycardia at a rate of 170 per minute He was given intravenous lidocaine in boluses of 100 mg to a total of 400 mg and diphenylhydantoin 100 mg intravenously with success and was finally cardioverted with 10 watt seconds to normal sinus rhythm When in sinus *rhythm the electrocar*diogram showed evidence of an anterior wall myocardial infarction and ST elevation suggestive of a ventricular aneurysm

Physical examination with the patient in sinus rhythm revealed a paradoxical pulsation at the cardiac apex and loud S3 and S4 gallop sounds

Chest roentgenogram revealed a calcified aneurysm of the left ventricle

The patient was digitalized and placed on procainamide 500

ing every 6 hours and remained in sinus rhythm without premature ventricular contractions On the fifteenth hospital day he exhibited bigeminal rhythm and digoxin was withheld because of the possibility of digitalis intoxication On the following day the patient was found to have a heart rate of 160 per minute

The electrocardiogram showed ventricular tachycardia Carotid sinus pressure was applied in succession to the right and left carotid bodies with no change in the arrhythmia Then a blow to the midsternum was given with no effect on the arrhythmia The area of paradoxical pulsation was then delineated and a sharp blow to this area abruptly converted the ventricular tachycardia to normal sinus rhythm as shown in Fi 2. The arrow points to the timing of the blow

The stimulus to the chest evoked an early ventricular depolarization distinctly different in morphology from the preceeding QRS The first atrial beat had a shorter P R interval followed by normal sinus rhythm

The same afternoon the patient had another episode of ventricular tachycardia despite intravenous lidocaine This episode was successfully terminated with a similar blow over the area of parodoxical pulsation He was then started on oral di opyramide phosphate with good results The patient refused further evaluation and was discharged home

Discussion

Two cases are presented with recurrent ventricular tachycardia in the setting of anterior wall left ventricular aneurysm Both patients failed to respond appropriately to drug therapy and were successfully treated by a blow to the area of maximal paradoxical pulsation Indiscriminate blows to the chest wall were unsuccessful in these patients despite previous reports of successful conversion of ventricular tachycardia

A chest blow has been reported previously to be effective in restoring a palpable pulse in patients with Stokes Adams attacks[5] and other forms of cardiac arrest This maneuver has also been reported as being effective in converting ventricular tachycardia in the setting of coronary artery disease We have found chest thump to be relatively ineffective in converting ventricular tachycardia in individuals with left ventricular aneurysm when the blow is delivered to any region of the precordium but have found that when the blow is directed to the area of maximal paradoxical pulsation that this modality of low energy cardioversion is quite effective This report presents two patients having 3 episodes of ventricular tachycardia so treated

It has been said that the mechanism by which a low energy mechanical impulse such as a blow to the anterior chest depolarizes part of the re entry pathway the probable basis for most cases of clinical ventricular tachycardia

It seems then that a blow to any area of the precordium may not alter the regions involved in the re-entry sequence If a blow to the area of maximal paradoxical pulsation appears to be effective it implies that the aneurysm itself either gives rise to the ectopic impulse or makes up an important portion of the re entrant route The depolarization of this region creates temporary local block which prevents further conduction

This mechanism of local delay may also be operative in the action of certain drugs as suggested recently[7] Procainamide delays the coupling interval of the ventricular premature depolarization until the arrhythmia disappears This effect is more apparent as the blood level of the drug increases

Mechanical stimulation by chest blow is advocated only as an initial intervention which carries low risk which can be performed at the bedside and can always be followed by more definite treatments such as direct current cardioversion or drug therapy

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Clinical pathologic conference

Duchenne's muscular dystrophy

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DR SHIRLEY RUBLER The patient was a 23 year old black male whose illness began in 1959 when at age five years, his parents noticed leg weakness difficulty in climbing stairs and increased size of calf muscles He had two brothers one of whom died at age 20 with a similar muscular disorder and another with brain damage due to birth trauma Six sisters were well Genetic information regarding maternal male relatives was not available

On admission to the Hospital of the University of Pennsylvania in 1964, the patient had a waddling gait but was still able to play with his peers despite dyspnea on climbing a flight of stairs Symmetrical weakness primarily involved the shoulder and pelvic girdles and flexor and extensor muscles of the neck The biceps triceps and thigh flexors were also affected the muscles of the shoulder girdle were atrophic but the calf muscles were enlarged (pseudo hypertrophic) Cardiac examination disclosed a normal left ventricular impulse and a short localized Grade II/VI apical systolic murmur There was sinus tachycardia at 120 beats per minute and a blood pressure of 105/75 mm Hg A right deltoid muscle biopsy demonstrated myopathy with regeneration The SGOT was 168 units A diagnosis of X linked recessive Duchenne s progressive muscular dystrophy was made

After discharge there was progression of weakness resulting in confinement to a wheelchair in 1968 and to bed by 1972 An admission to the Philadelphia General Hospital in May 1974 was for cough sore throat and the sudden onset of dyspnea Deep tendon reflexes were uniformly absent and there was bilateral foot drop On cardiac examination third and fourth heart sounds were audible and there was sinus tachycardia of 120 beats per minute Chest x ray showed mild pulmonary venous congestion and a moderately enlarged globular cardiac silhouette Dyspnea persisted despite digitalis Laboratory study revealed CPK of 68 to 113 units LDH of 105 units SGOT of 30 units and SGPT of 114 units LDH isoenzyme fractionation showed LDH$_1$ 26 69 per cent LDH 26 02 per cent LDH$_3$ 21 28 per cent LDH 12 5 per cent and LDH$_5$ 13 5 per cent

In July 1975 the patient was readmitted to the Philadelphia General Hospital with the abrupt onset of palpitations commencing shortly before arrival in the emergency room For the preceding six weeks he had experienced several brief bouts of syncope On admission he was diaphoretic and dyspneic and was found to be in supraventricular tachycardia with a ventricular rate of 210 to 270 beats per minute (Fig 1) Tensilon and carotid massage temporarily slowed the arrhythmia which recurred but ceased with the administration of propranolol A brief period of hypotension and bradycardia (30 to 40 beats per minute) followed reversion to sinus rhythm Examination then revealed respirations of 24 to 28 per minute and a blood pressure that stabilized at 118/70 mm Hg There was exaggerated lumbar lordosis with wasting and marked weakness of the muscles of thorax of shoulder and pelvic girdles as well as the flexors and extensors of the neck The calf muscles were pseudohypertrophied The deep jugular veins exhibited large A waves Carotid

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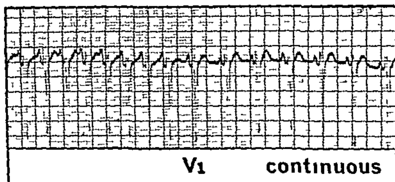


Fig 1 Electrocardiogram (Lead V) demonstrating supraventricular tachycardia with varying degrees of atrioventricular block and ventricular response of 135 to 215 beats/min

pulsations were diminished but equal Fine crepitant rales were present at both lung bases On cardiac examination there was a diffuse left ventricular impulse at the anterior axillary line in the sixth intercostal space a right ventricular impulse at the left sternal border third and fourth heart sounds and a Grade 3/6 apical holosystolic murmur The electrocardiogram showed sinus tachycardia at a rate of 120 beats per minute a P R interval of 0 20 second a frontal plane QRS axis of 110 degrees biatrial abnormalities nonspecific ST T wave changes and in Lead V an R/S ratio of 1 7 and an R wave of 17 mm (Fig 2) A vectorcardiogram (Fig 3) two weeks later revealed prominent initial anterior forces 30 msec in duration In the horizontal plane the maximum anterior vector was 1 8 mv the maximum posterior vector was 2 2 mv and the inscription was counterclockwise In the frontal plane the QRS loop was inscribed in a clockwise direction and was directed inferiorly with large terminal rightward forces and a maximum vector of 2 mv Chest x ray (Fig 4) showed striking globular enlargement of the heart with a prominent right cardiac sweep The diaphragms were not elevated An echocardiogram revealed only equivocal evidence of pericardial effusion Pulmonary scan with technetium labeled macroaggregated albumin showed segmental defects in the left lung field and decreased perfusion of the right middle and lower lobes Three days after admission the patient expectorated blood tinged sputum and anticoagulants were instituted Tachycardia persisted Therapy with digoxin quinidine and diuretics was maintained upon discharge

The third and final admission to the Philadelphia General Hospital in September 1975 was occasioned by three weeks of pedal edema treated with diuretics by a home care physician Two days before admission the patient developed right sided chest pain that was sharp nonradiating accentuated by deep inspiration accompanied by dyspnea orthopnea and cough productive of blood tinged sputum and followed by chills and a feverish sensation On admission temperature was 100° F pulse 120 beats per minute respiration 24 to 28 per minute and blood pres

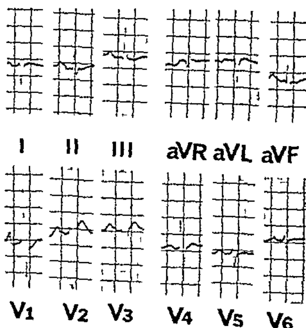


Fig 2 Electrocardiogram demonstrating in Lead V a tall R wave (17 mm) with an R/S ratio of 1 7 and an abnormal P wave Frontal plane axis is 110 degrees with nonspecific ST and T wave changes and prolonged PR interval of 0 20 second

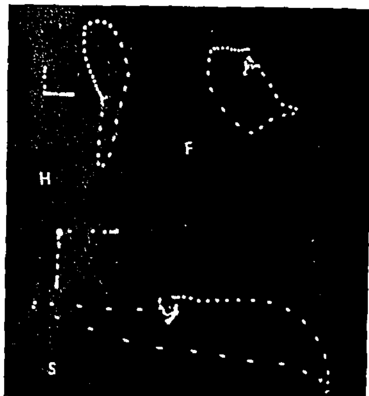


Fig 3 Vectorcardiogram with exaggerated anterior forces 30 msec in duration Horizontal loop is inscribed in counterclockwise fashion while in the frontal plane the QRS loop is clockwise and directed inferiorly with large terminal rightward forces

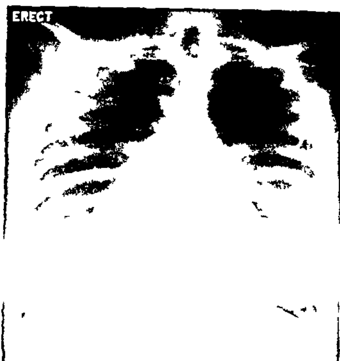


Fig 4 Chest x ray The striking globular enlargement of the heart is apparent and there is a prominent right cardiac sweep

sure 118/80 mm Hg There were prominent A and V waves in the jugular venous pulse Examination of the chest disclosed diminished breath sounds over the right lung field dullness to percussion over the lower right chest posteriorly accompanied by egophony

On cardiac examination the left ventricular impulse was displaced and diffuse and there was a prominent right ventricular impulse The second sound was palpable at the left base Third and fourth heart sounds were again audible A Grade III/VI holosystolic murmur was heard at the lower left and right sternal borders and augmented during inspiration The electrocardiogram showed sinus tachycardia of 108 beats per minute a frontal plane QRS axis of 115 degrees a PR interval of 0 24 second an R wave of 13 mm and an R/S ratio of 1 2 in V_1 and conspicuous Q waves in Leads I aVL and $V_{5,6}$ (Fig 5) The T waves were low voltage or isoelectric in both standard and precordial leads Chest x ray revealed marked globular cardiomegaly a right pleural effusion, vascular redistribution to the upper lobes and a left lower lobe infiltrate

Pulmonary scan disclosed no significant change from July 1975 Pulmonary angiography showed interruption of segmental arteries to both right and left lower lobes consistent with pulmonary embolization LDH was 424 units Red blood cells were 3 32 million/cu mm hematocrit 32 3 per cent, hemoglobin 10 2 Gm per cent white blood cells 23,700/cu mm with 89 per cent polymorphonuclear leukocytes

Five days after admission the patient developed sharp left sided abdominal pain and increasing jugular venous distention Rales were heard at both bases and a left pleural effusion appeared Urinary output decreased melena developed and two days later he became hypotensive bradycardiac and died

Dr Joseph K Perloff will now discuss the clinical aspects of this case

Dr Perloff The diagnosis of X linked recessive Duchenne s progressive muscular dystrophy was well established Let me comment on the information in the order presented by Dr Rubler The patient was a male who at age five years developed weakness of his legs difficulty climbing stairs and increased size of calf muscles A brother had a similar muscular disease but six sisters were spared Classic Duchenne s dystrophy is a sex linked recessive disorder characteristically beginning in the first five years of life transmitted by the mother to her son(s) as overt disease (as in this patient and his brother) and to

50 per cent of daughters as an asymptomatic carrier state Serum enzymes and occasionally a distinctive electrocardiogram (see below) have proved useful in identifying carrier females but this information was not available from the sisters and mother of the patient under consideration Initial involvement of the pelvic girdle and lower extremities causes a clumsy waddling gait and difficulty climbing stairs and rising from the floor or a chair Pseudohypertrophy of the calves is especially marked early in the course of the disease Calf muscles are larger than normal but weak because of extensive deposition of connective tissue and fat On admission to the Hospital of the University of Pennsylvania in 1964 effort dyspnea was described but in such patients the effort needed to accomplish even simple maneuvers may provoke *non cardiac* dyspnea and fatigue The shoulder girdle was now involved a pattern typical of the spread of the dystrophic process A deltoid muscle biopsy was histologically abnormal but not diagnostically specific which is often the case The SGOT was elevated reflecting the characteristic release of skeletal muscle enzymes in active Duchenne s dystrophy The cardiac examination was normal (the short soft apical systolic murmur was probably innocent) but there was sinus tachycardia Inappropriate labile sinus tachycardia is common in Duchenne s dystrophy although the mechanism remains unclear Preliminary studies of autonomic regulation of the heart in Duchenne s dystrophy disclosed the combination of excessive rate acceleration after atropine followed by effective slowing with propranolol These results seemingly discount the role of the parasympathetic nervous system and implicate augmented sympathetic activity as the cause of resting tachycardia in Duchenne s dystrophy After discharge progression of weakness resulted in confinement to a wheelchair by age nine years and to bed by age thirteen years Progressive deterioration generally culminates in a wheel chair existence by age twelve years The patient was readmitted to the Philadelphia General Hospital with cough and sudden dyspnea Dystrophy of chest muscles and diaphragm compromise respiratory function and predispose to pulmonary infections but cardiac failure (myocardial dystrophy) may coexist and be primarily responsible for cough and dyspnea Deep tendon reflexes were absent which is almost

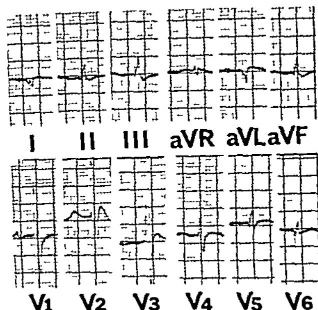


Fig 5 Electrocardiogram displays prolonged PR interval of 0 24 second a Lead V R wave of 13 mm and R/S ratio of 1 2 Conspicuous Q waves in Leads I aVL and V_{1-4} are present. T waves are of low amplitude throughout

always the case at this stage of the disease Cardiac examination now revealed third and fourth heart sounds (both probably abnormal) but certainly the fourth sound at this age) and once again persistent sinus tachycardia These observations together with radiographic evidence of pulmonary venous congestion and cardiac enlargement would appear to identify myocardial involvement but high diaphragms due to diaphragmatic dystrophy can result in a globular cardiac silhouette and increased soft tissue densities resembling pulmonary venous congestion The high CPK LDH SGOT and SGPT attest to systemic myopathic disease that was still active and progressive The LDH isoenzymes showed approximately twice the concentration of LDH_1 as LDH_2 Does the increased concentration of LDH_1 (presumably the fast moving anodal fraction) represent selective release of this isoenzyme from myocardium? Probably not Although *skeletal* muscle enzymes are copiously released into plasm in Duchenne s dystrophy the use of enzyme quantification has not been successful in detecting myocardial involvement It was hoped that the distinctive profiles of LDH isoenzymes might identify active myocardial dystrophy However the isoenzyme profile of dystrophic skeletal muscle resembles that of cardiac muscle

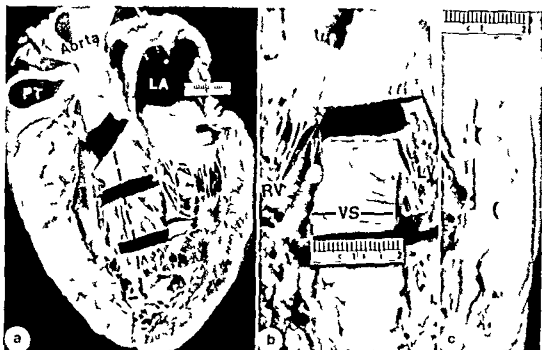


Fig 6 Gross photographs of heart *a* View of interior of left ventricle The dashed black line is where the cut was made from which *b* was taken The left ventricle and left atrium *(LA)* are dilated *PT* = pulmonary trunk *b* *Longitudinal* section of ventricular septum *(VS)* which is free of foci of fibrosis and necrosis *RV* = right ventricle *LV* = left ventricle *c* Longitudinal cut of posterior left ventricular free wall Its thickness is considerably less than that of the ventricular septum

thus compromising the specificity of these determinations[4] Even coronary sinus catheterization did not convincingly document myocardial release of enzymes[4]

Readmission in July 1975 was for supraventricular tachycardia with a ventricular rate of 120 to 270 beats per minute Carotid sinus massage transiently slowed the rate permitting identification of a P wave preceding each QRS confirming that the arrhythmia was supraventricular tachycardia and not atrial flutter Reversion to sinus rhythm was accompanied by bradycardia and hypotension suggesting a sick sinus node and perhaps accounting for the brief bouts of syncope during the preceding six weeks In this regard narrowing of intramural coronary arteries—especially those supplying sinus and atrioventricular nodes—is known to occur in classic Duchenne s dystrophy[5] A variety of arrhythmias have been observed in addition to the inappropriate sinus tachycardia mentioned above Supraventricular tachycardia is uncommon but atrial and ventricular premature beats atrial flutter paroxysmal ventricular tachycardia and excessive myocardial irritability during cardiac catheterization are well established[4, 6] On this admission widespread dystrophy was again described but pseudohypertrophy was confined to the calves Pseudohypertrophy typically involves the gastrocnemius and spares other muscle groups but occasionally the deltoids pectorals and neck muscles are similarly affected[3] The large A wave in the jugular venous pulse was probably a combination of A and V waves simultaneous because of tachycardia and a relatively long P R interval (Fig 2), and tall because of right ventricular failure precipitated or aggravated by supraventricular tachycardia The decreased carotid pulses reflected a low stroke volume secondary to depressed left ventricular function and rapid heart rate Further evidence of left ventricular failure was provided by bilateral crepitant basal rales a left ventricular impulse at the anterior axillary line and third and fourth heart sounds which were appreciated as distinct sounds separately rather than in summation despite the rapid heart rate and relatively prolonged P R interval In judging left ventricular size by precordial palpation the height of the left leaf of the diaphragm must be taken into account (diaphragmatic dystrophy) A high left diaphragm causes the left ventricular impulse to assume both a lateral and a *superior* position but in this patient the impulse was at the anterior axillary line in the *sixth* intercostal space (not elevated) indicating intrinsic dilatation and not displacement The right ventricular impulse may



Fig 7 Histologic sections of posterobasal portion of left ventricular free wall *(a b c)* and ventricular septum *(d)* *a* Subendocardial scar *b* Subepicardial scarring *c* Scarring in mid portion of wall *d* No scarring at all in the septum (Hematoxylin and eosin stain each magnification ×40)

have been due chiefly to a decrease in anteroposterior chest dimensions commonly found in patients with Duchenne's dystrophy Thoracic bony abnormalities result from wasting and weakness of thoracic muscles as seen in this patient The Grade 3/6 holosystolic apical murmur was almost certainly mitral regurgitation which in this setting can be due to left ventricular failure per se or to involvement of a papillary muscle (generally posterior) and contiguous left ventricular wall (dystrophic papillary muscle dysfunction)

We now come to a very important item the scalar electrocardiogram (Fig 2) Persistent sinus tachycardia has already been commented upon The prolonged PR interval (0 20 sec at a rate of 120 per minute) may have been related to narrowing of the coronary artery supplying the atrioventricular node I look forward to Dr Roberts comments on the small intramural coronary arteries especially those to sinus node (see above) and A V node There were biatrial abnormalities (broad notched P wave in Lead II and a tall peaked P wave in Lead V) Both of these changes could have been the immediate sequelae of rapid supraventricular tachycardia This contention is supported by the electrocardiogram taken on the next admission (see below) at which time the P wave in Lead V was no longer tall and peaked the left atrial abnormality in Lead II was less marked but still present and may have been due to mitral regurgitation Thus the tall A wave the right ventricular impulse on palpation and the tall peaked P wave in Lead V can be explained without invoking pulmonary hypertension which has not been present in catheterized patients with Duchenne's dystrophy If pulmonary hypertension were absent what then is the explanation for the Lead V_1 R wave of 17 mm and R/S amplitude ratio of 1 7 together with a vectorcardiogram (Fig 3) showing prominent initial anterior forces with *counter clockwise inscription* in the horizontal plane? In right ventricular hypertrophy the horizontal vector loop is frequently clockwise whereas in Duchenne's dystrophy the horizontal loop is virtually never clockwise despite the prominence of anteriorly directed forces A variety of heredofamilial neuromyopathic disorders are associated with abnormal electrocardiograms but only the classic sex linked pseudohypertrophic dystrophy of Duchenne results in a distinctive electrocar

diographic pattern[1] Thus the most frequent and reliable index of cardiac involvement is the scalar electrocardiogram the vectorcardiogram serves as a useful supplement in this regard Tall right precordial R waves with increased R/S amplitude ratios and deep limb lead and lateral precordial Q waves form a distinctive motif that is related specifically to one particular type of neuromyopathic disease—the classic pseudohypertrophic sex linked dystrophy of Duchenne manifested by the patient under consideration (Fig 2 Fig 5) Affected siblings often exhibit similar if not identical tracings and distinctive Duchenne patterns have been found in female carriers who have only enzyme evidence of systemic myopathic disease The existence of characteristic electrocardiograms in classic Duchenne s dystrophy is no longer debated but their mechanism is Studies thus far have made it clear that these characteristic patterns are not related to thoracic deformity thoracic muscle atrophy pulmonary hypertension hypertrophy of the right ventricle crista supraventricularis or interventricular septum or to abnormalities in right ventricular conduction or to coexisting abnormalities of small intramural coronary arteries[1] Two theories prevail one that the electrocardiographic pattern reflects acquired dystrophic myocardial disease the sites of which are genetically regulated and the other that the morphology of the electrocardiogram represents persistence of the patterns of infancy and early childhood[8] My observations are not consonant with the idea that the distinctive QRS in Duchenne s dystrophy represents persistence of infantile or childhood patterns What alternative theories can then be proposed? It could be argued that the occurrence of identical electrocardiograms in siblings implies a genetic determinant of the distinctive electrophysiologic patterns This genetic determinant might result in either focal anatomic lesions in the heart or electrical alterations *without* detectable anatomic counterparts A purely *electrical* explanation is essentially speculative An *anatomic* basis for the anterior shift of the QRS and deep Q waves would mean that virtually identical zones of myocardium were preselected for dystrophic changes by a genetic determinant Despite the fanciful nature of this concept some evidence suggests that it may be so The prominent anterior forces may represent a relative loss of posterobasal electrical activity as in strictly posterior myocardial infarction,[4] [1] and the Q waves may reflect lateral or diaphragmatic extension of the dystrophic zone One necropsy study done together with Dr Roberts lends credence to this theory The present case may provide further electrocardiographic-vectorcardiographic necropsy correlations

Now to return to Dr Rubler s account after this long but important digression on the electrocardiogram The chest x ray (Fig 4) showed striking globular enlargement of the cardiac silhouette not due to elevated diaphragms or on echocardiographic study to pericardial effusion Recall that this patient s illness began at age five years but *overt* congestive failure did not occur until the July 1975 admission 16 years later when he presented with rapid supraventricular tachycardia This is a familiar time course Rapidly progressive heart failure may follow years of circulatory stability during which the only suspicion of cardiac involvement is found in the electrocardiogram The pulmonary scan and blood tinged sputum that Dr Rubler describes imply pulmonary embolism a *relatively common* occurrence in congestive heart failure but much more so in the presence of peripheral edema which was described by the home care physician prior to the third and final admission In addition prolonged immobilization in a wheelchair with legs dependent and knees flexed further predisposes to pulmonary emboli The description of the last admission to the Philadelphia General Hospital underscored the clinical diagnosis of pulmonary emboli—right sided pleuritic chest pain hemoptysis with diminished breath sound dullness to percussion and egophony over the right posterior lung base It should not be forgotten however that patients with Duchenne s dystrophy often succumb to pulmonary *infection* to which they are especially susceptible because of weakness of thoracic and diaphragmatic muscles together with thoracic bony deformities (scoliosis pectus excavatum loss of thoracic kyphosis)[1] On physical examination the prominent right ventricular impulse the palpable second sound at the left base and the new murmur of tricuspid regurgitation (holosystolic at the lower left and right sternal borders augmented during inspiration) are in accord with a recent rise in right ventricular pressure due to pulmonary emboli The prominent A and V waves

in the jugular pulse are appropriate for right ventricular failure with tricuspid regurgitation although comment was not made on the Y descent which is usually attenuated or abolished in this setting The electrocardiogram has in part been commented upon but it is worth underscoring the presence of the anterior shift of the QRS as well as the now conspicuous Q waves in Leads I aVL and V_5 (Fig 5) It would therefore anticipate that Dr Roberts will find myocardial dystrophy not only in the posterobasal wall of the left ventricle (tall R wave and increased R/S amplitude ratio in Lead V_1) but also in the lateral wall (Q waves in Leads I aVL and lateral precordium) The small Q wave in Lead II was not present in the previous electrocardiogram but alone is not sufficient to infer that the inferior left ventricular wall is involved These initial force abnormalities in the electrocardiogram are not the result of coronary artery disease The large extramural coronary arteries should be entirely normal in such a young patient and previous studies have shown no relationship between the presence and degree of narrowing of intramural coronary arteries and the location and degree of myocardial scarring The chest x ray in addition to marked cardiomegaly showed a right pleural effusion and a left lower lobe infiltrate appropriate for pulmonary emboli and vascular redistribution to the upper lobes a hallmark of high pulmonary venous pressure in this case due to left ventricular failure The lung scan was unchanged but a pulmonary arteriogram was typical of bilateral pulmonary emboli Elevation of LDH probably reflected skeletal release of this enzyme because the muscular dystrophy was still chronically active The total white blood cell count was very high and the differential count showed a marked shift to the left (89 per cent polymorphonuclear leukocytes) suggesting infection but in accord with pulmonary infarction Preterminally the patient developed abdominal pain and melena which seemed to have been the immediate or precipitating cause of death There are a number of reports of deaths in progressive muscular dystrophy following brief episodes of abdominal pain One patient personally seen died elsewhere after laparotomy for severe abdominal pain of unknown cause There has been no evidence of involvement of smooth muscle of the gastrointestinal tract in Duchenne's dystrophy The only known smooth muscle that is affected in this disorder is the media of small intramural coronary arteries Melena has not been described as an accompaniment of the puzzling abdominal pain although diarrhea and vomiting have occurred Was this patient still on the anticoagulants begun in the July 1975 admission?

And now Dr William C Roberts

Dr Roberts The heart in the present patient is very similar to that in the other two patients previously reported by Dr Perloff and associates The heart weighed 500 Gm All four chambers were dilated but particularly the two ventricles The right atrium was larger than the left atrium The endocardium at the apex of the left ventricle was focally thickened by fibrous tissue The ventricular septum measured up to 1 7 cm in thickness and the left ventricular free wall up to 1 1 cm in thickness Focal scarring was observed grossly in the left ventricular free wall posterolateral portion The scarring was mainly subendocardial (inner one half) in location but toward the apex a small transmural (more than inner one half) scar was present Probable patchy scars were present grossly in the right ventricular free wall Except for focal thickening of the margin of the anterior mitral leaflet the four cardiac valves were normal The mitral anulus measured 12 cm (average normal = 9 cm) and the tricuspid valve anulus 11 5 cm (average normal = 11 cm) in circumference The coronary arteries were free of atherosclerotic plaques

Histologically focal scars were present in the posterolateral left ventricular free wall and also in the right ventricular free wall The scars were located mainly in the subendocardium midventricular wall and subepicardium (Fig 6) Multiple sections of ventricular septum disclosed no myocardial scarring at all (Fig 7) No foci of acute necrosis were present in multiple sections of myocardial wall Three small arteries in the area of the atrioventricular node showed thick walls and narrowed lumina The intramural coronary arteries in the free walls of both right and left ventricles and in the ventricular septum appeared normal

The heart in this patient illustrated findings described previously in patients with Duchenne's muscular dystrophy (1) dilatation of both ventricles (2) patchy but fairly extensive scarring in both subendocardial and subepicardial locations within the posterolateral left ventricular

free wall without narrowing of the extramural coronary arteries (3) absence of scarring within the ventricular septum (4) thickening of the walls and narrowing of the lumina of a few intramural coronary arteries and (5) absence of *myocardial necrosis and inflammation*

In addition to the above findings the present patient had focal scars within the right ventricular free wall Scarring in this location is quite unusual in the absence of elevation of right ventricular systolic pressure, and there was no indication of right ventricular systolic hypertension in our patient except possibly terminally in response to pulmonary emboli

The occurrence of a ventricular septum which is clearly thicker than left ventricular free wall (ratio 1 5 1), which occurred in our patient, indicates that the patient had *asymmetric septal hypertrophy* (ASH) Therefore another condition should be added to the list of causes of ASH Our patient however did not have disorientation of myocardial fibers in the ventricular septum, and the ventricular cavities were dilated Thus although our patient had ASH he did not have hypertrophic cardiomyopathy It is presumed that the thinning of the posterobasal portion of left ventricular free wall was the consequence of myocardial scarring in this area It is probable that the left ventricular free wall was of similar thickness to the ventricular septum earlier in life Thus the occurrence of disproportionate septal thickness in our patient is an example of acquired ASH Possibly serial echocardiograms in these patients could document the development of the thinning of the posterobasal portion of left ventricular free wall

In addition to the cardiac findings the left lung was collapsed and had a black-brown discoloration and consolidation of the lower lobe The arteries of this lobe contained multiple organized emboli Similar changes were noted in the right upper lobe and again there were emboli Atherosclerosis (mild) of the pulmonary arteries was noted Massive infarction congestion and heart failure cells were observed on microscopic examination

The gastrointestinal tract was free from pathology The liver was enlarged firm, and dark brown and on cut surface had a nutmeg appearance Microscopic findings included acute and chronic passive congestion with collapse of the reticulum

Final diagnosis

Clinical Classic Duchenne s progressive muscular dystrophy *Dystrophic cardiomyopathy* with supraventricular tachycardia and biventricular failure Pulmonary emboli

Pathologic Dystrophic cardiomyopathy involving the posterolateral left ventricular wall Small vessel coronary artery disease in the region of the AV node Multiple pulmonary emboli Chronic passive congestion of the liver

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Fundamentals of clinical cardiology

Management of the patient with renovascular hypertension

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Information from clinical and experimental investigations during the past two decades allows the clinician to pursue a more rational approach to the diagnosis and management of the patient with hypertension resulting from renovascular disease Methods of detecting these lesions have been established In particular aortorenal angiography and the determination of renal venous renin activity levels under controlled conditions have contributed materially to the favorable results after renovascular surgery in the selected patient However the clinical use of newer more potent medications that inhibit renin release or otherwise interfere with the renin-angiotensin-aldosterone hormonal system offers great potential in medical therapy

Patients with renovascular hypertension the most common cause of secondary arterial hypertension are not a homogeneous group The estimated 5 per cent of the hypertensive population that have renal artery stenosis as the underlying cause of elevated blood pressure is largely comprised of two groups of patients those with atherosclerotic disease and those with the non atherosclerotic fibrous and fibromuscular stenoses Thus the type location and severity of renal and renovascular lesions as well as associated disease processes are most important in determining the management of such patients

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Pathologic features

Atherosclerotic renovascular disease Atherosclerotic plaques may compromise the ostium of one or both renal arteries or such atheromatous plaques may be located in the renal artery itself usually in the proximal third of the vessel (Fig 1) In either instance the disease process may progress ultimately causing complete occlusion of the involved vessel Both renal arteries generally are involved Multiple areas of atherosclerotic narrowing are not uncommon In a high percentage of patients with atherosclerotic stenoses as well as in those with fibromuscular disease fusiform poststenotic dilatation of the renal artery is observed and on rare occasions the dilatation may be such that angiographically and pathologically it resembles an aneurysm of the renal artery Because atherosclerotic lesions of the renal artery are generally local manifestations of widespread atherosclerosis atheromatous disease frequently will be observed in the aorta and elsewhere [2]

Fibromuscular disease Recently Harrison and McCormack[3] classified nonatherosclerotic stenoses on the basis of the arterial layer—intima media or adventitia—in which the lesions predominate and on whether there is fibroplasia hyperplasia dissection or aneurysm formation (Fig 2) Medial dissection (5 per cent of patients) usually is clearly distinguishable on the renal arteriogram Medial fibroplasia (60 to 70 per cent of patients) and the rare medial hyperplasia (less than 5 per cent) generally are seen as multifocal stenoses in which there are large aneurysms or beads that exceed the expected diameter of the renal artery because of extensive mural thinning

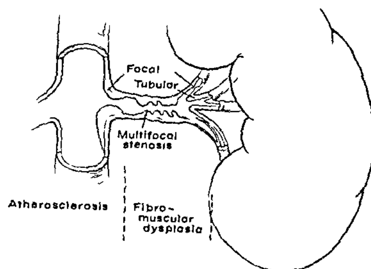


Fig 1 Schematic representation of type and location of renal artery occlusive disease

Lesion predominantly	Types
Intimal	INTIMAL FIBROPLASIA
Medial	(MEDIAL) FIBROMUSCULAR DYSPLASIA (Focal multifocal or tubular stenoses with or without aneurysm) (a) Medial fibroplasia (b) Perimedial fibroplasia (c) Medial hyperplasia (d) Medial dissection
Adventitial and periarterial	PERIARTERIAL FIBROPLASIA

Fig 2 Types of idiopathic fibrous and fibromuscular stenosis of the renal artery (From Harrison E G Jr and McCormack L J Pathologic classification of renal arterial disease in renovascular hypertension Mayo Clin Proc 46 161 1971 Reproduced with permission)

between thickened fibromuscular ridges Perimedial fibroplasia (15 to 20 per cent of patients) is characterized by a generalized but irregular thickening of the outer media which may simulate multifocal stenosis and beading but the diameter of the beads is less than that of the uninvolved renal artery The intimal and adventitial lesions are rare (1 to 2 per cent) and generally are focal or tubular stenoses In contrast to atheromatous disease fibromuscular stenoses characteristically involve the distal portion of the renal artery and its branches (Fig 1)

Fibromuscular changes have been found in most arteries in addition to the renal artery notably the carotid arteries where they may cause symptomatic stenoses Additionally, some investigations have found an associated high incidence of intracranial berry aneurysms in patients with fibromuscular renal artery disease[4, 5]

Pathophysiologic features

Systemic hypertension is the physiologic consequence of stenosis of the renal artery (arteries) in the patient with renal artery disease A number of concepts in the pathophysiology of renovascular hypertension have evolved during the past several years from the pioneering work of Goldblatt[6] in experimental hypertension

Experimentally there are two forms of renovascular hypertension In the first a renal artery is constricted, reducing the blood flow to that kidney and causing ischemia The contralateral kidney is left untouched In the second form a renal artery is constricted but the opposite kidney is removed Hence these models of renovascular hypertension are termed one clip two kidney Goldblatt hypertension and one clip one kidney Goldblatt hypertension, respectively Both animal models become hypertensive to a similar degree, but important differences exist in the pathophysiologic mechanisms

The renin-angiotensin-aldosterone hormonal system has been established as an integrated capacity-volume system of major importance in the control of arterial blood pressure In the one clip one kidney experimental model the plasma renin activity level may be normal or reduced and the renin content in the kidney reduced However, in the one clip two kidney hypertension model there are increased or, in the presence of hypertension inappropriately high plasma renin activity levels increased renal renin content in the ischemic kidney (on the side of renal artery constriction) and a reduced renin content in the contralateral kidney The role of renin and therefore of its physiologic consequence—vasoconstriction—has been further investigated by the use of special tools antirenin serum antibodies to angiotensin II, and specific peptide inhibitors of angiotensin II

Administration of these agents lowers the blood pressure in the one clip two kidney hypertension model but not in the one clip one kidney hypertensive animals[7, 8] However if the latter group is

first prepared by sodium depletion the above maneuvers lower the blood pressure in this group as well[1] The effect of sodium depletion in lowering blood pressure in the one clip one kidney model while not affecting the one clip two-kidney form was first demonstrated by Swales and colleagues[11] Consequently these two experimental models of renovascular hypertension may be viewed as renin dependent or vasoconstriction mediated in one clip two kidney hypertension and as sodium or volume dependent in one clip one kidney hypertension Retention of salt and water by the ischemic kidney in the one clip one kidney model causes volume expansion and hypertension and results in suppression of the renin dependent vasoconstriction manifested in the one clip two kidney model However their common basis is unmasked by sodium restriction whereby the volume dependent form is converted to a vasoconstriction renin dependent form

Current research emphasizes the possibility of a role for depressor substances in the development of hypertension Further investigation into the role of prostaglandins and kinins may disclose important interactions with pressor systems such as the renin–angiotensin–aldosterone hormonal system which already has been shown to have a central role

The mechanisms proposed for these experimental models occur in human renovascular hypertensive disease and the understanding of these principles provides a basis for the diagnostic evaluation and selection of therapy for these patients[8]

Clinical characteristics

The review of the clinical characteristics of patients with documented renovascular hypertension by Simon and associates for the Cooperative Study of Renovascular Hypertension examined in detail the thesis that hypertension associated with unilateral renal disease curable by surgery had distinctive characteristics

The task of the clinician in differentiating the patient with renovascular hypertension from the large pool of patients with essential hypertension is difficult because no one characteristic or combination of characteristics is diagnostic Of the many characteristics that have been suggested a few have become important markers for renovascular hypertension Patients with renovascular hypertension are not a homogeneous group patients with fibromuscular disease as a group differ in many characteristics from those patients with atherosclerotic renal artery disease

Table I Urographic signs suggesting renovascular disease in hypertensive patients

1	Decreased renal size—disparity in renal pole to pole diameter of > 1 5 cm
2	Unilateral delay in appearance time of the contrast medium in the pelvic calyceal collecting system of the involved or more severely involved kidney in the early films
3	Late hyperconcentration of contrast medium
4	Ureteral notching suggesting the presence of pelvic-ureteral collateral vessels
5	Delayed washout of pelvic calyceal contrast medium with diuresis
6	Nonfunctioning kidney on excretory urogram with normal retrograde pyelogram
7	Defect in renal silhouette suggestive of segmental renal infarction

Generally the group with hypertension secondary to fibromuscular disease is younger has more females than males is more likely to have no family history of hypertension and is less likely to have target-organ damage (heart central nervous system kidneys) than is the group with essential hypertension or atherosclerotic renovascular disease In the former group upper quadrant abdominal or flank bruits of systolic–diastolic or continuous nature are common being heard in as many as 70 per cent of patients with fibromuscular disease Because of multivessel involvement in this disease a search should be made for other vascular bruits The isolated abdominal bruit that is only heard in systole is not correlated with the presence of a stenotic renal vessel Funduscopic examination commonly reveals less severe retinal artery changes—changes limited to narrowing and focal constriction (angiospastic) or retinal arteriosclerosis without exudates or papilledema that is Groups 1 and 2 of the Keith Wagener Barker classification

In contrast patients with renovascular hypertension due to atherosclerosis are older and frequently have a family history of hypertension or its sequelae Often they have severe retinopathy and target-organ damage Most of the patients with atherosclerotic renovascular hypertension are males

Patients with atherosclerotic renal artery disease frequently have considerable systemic vascular disease at the outset Those with more severe renal artery involvement have a much higher incidence of symptomatic coronary, cerebrovascular abdominal aortic, and peripheral vascular disease, which often may necessitate surgical management Additional symptomatic cardiovascular complications develop in a significant number of these patients as time passes [2]

Diagnostic investigations

A lack of agreement exists in regard to the extent of diagnostic evaluation of the hypertensive patient which is needed to distinguish essential hypertension from secondary causes

The history and physical examination often provide a basis for adequate suspicion In general the more severe the hypertension, the more frequent and severe the symptoms In any patient with severe hypertension, a renovascular cause should be considered

During the general examination, in addition to undergoing the routine laboratory tests the hypertensive patient should have a urinalysis, determination of serum electrolytes and determination of serum creatinine level as a measure of renal function before therapy is begun If the initial clinical assessment suggests that the hypertension is secondary or is moderate or severe or of recent onset (especially in the young patient who is likely to require long term antihypertensive therapy) further diagnostic investigations should be carried out

Rapid sequence excretory urography can provide useful anatomic-physiologic information in the search for renovascular causes of hypertension The cardinal manifestations of renovascular disease as displayed urographically are listed in Table I In the Cooperative Study of Renovascular Hypertension 11 4 per cent of 771 essential hypertensive patients had one of these signs, while 83 per cent of patients with significant stenosis had one or more abnormalities The urographic findings were normal in 16 7 per cent of patients with angiographically demonstrated stenoses Perhaps the most discriminatory urographic feature is that of either a diminished early nephrogram phase or a delayed appearance time on the involved side, 59 per cent of patients with significant stenoses had this sign, but only 2 per cent of those with essential hypertension did [19, 20]

In our experience, urographic abnormalities occur in approximately 70 per cent of patients with hypertension and severe renal artery stenosis The incidence is approximately 50 per cent in patients with moderate stenosis A difference in pole to pole diameter of the two kidneys of 1 5 cm or more occurs in approximately 60 per cent of patients with severe renal artery stenosis Of patients without such a difference in renal mass approximately 10 per cent have one or more of the other features Notching of the ureters (so called scalloping) by large collateral arteries is observed rarely, and almost invariably when this is seen, the underlying disease is fibromuscular dysplasia

In the further evaluation of the hypertensive patient, the radioisotope renogram can assess the separate function of the kidneys [18, 21] When patients are studied in the supine position and in the moderately hydrated state, a good qualitative correlation is found between the findings on an isotope renogram and the renal plasma flow, as determined by separated renal clearances of p aminohippurate Renographic abnormalities may not always indicate renal artery disease because such abnormalities may be due to other renal disease or anatomic variations Thus, the renogram should be considered a renal function test and not a screening procedure for renovascular disease It is best utilized in conjunction with the information obtained from excretory urography and clearance measurements In the individual patient the renogram can be a most useful qualitative test of the function of the separate kidneys both in the initial and follow up evaluations particularly after corrective renal artery surgery

Renal arteriography has evolved over the past 20 years to have a major role both in the diagnosis of renovascular disease and in the selection of candidates for surgical procedures Current techniques in which multiple projections selective renal artery injections, and magnification techniques are used provide accurate anatomic evidence for the detection or exclusion of renal artery obstructive disease [22]

In the past, the only procedure for assessing the significance and correctability of a renovascular lesion was that of separated renal function studies [3] These tests based on demonstrating excessive sodium and water reabsorption by the affected kidney, are technically complex requir

ing the urologist to place occlusive ureteral catheters and to use sophisticated laboratory support for the determination of standard renal clearances. However, this technique is a reliable tool in determining surgical correctability, and it remains in use in conjunction with measurements of renal pressor substances in some centers.[4]

The assessment of the functional significance of a renovascular lesion in causing high blood pressure involves the measurement of renal pressor substances. The proper determination of plasma renin activity in the individual renal veins and inferior vena cava is a highly reliable indicator of potential surgical relief of hypertension.[25] An important prerequisite for these studies is the avoidance of pharmacologic agents that may alter the renin-angiotensin-aldosterone system, such as the commonly used cyclic progestational agents or estrogens, diuretics, propranolol, methyldopa, clonidine, catecholamine depleting agents, and hydralazine. Particularly to be avoided are agents such as propranolol and methyldopa which interfere with renin release. Our present regimen is to stop the use of antihypertensive medications for 4 weeks before determination of renin activity (except for guanethidine, which may be used as needed to control severe hypertension[26]) to replete body potassium stores and to maintain the patient on a normal sodium diet (approximately 135 mEq/day). The patient then is placed on a program to effect acute sodium depletion, utilizing a diet of 20 mEq Na, 90 mEq K, and chlorothiazide 1 Gm/day. When a weight loss of 1.5 kilograms or more has been achieved, generally after 3 days, the patient undergoes venous catheterization by the Seldinger technique under fluoroscopic control to allow blood sampling for measurement of renin activity from the renal veins and low inferior vena cava. Lateralization of the renal vein renin activity as demonstrated by a ratio of 1.5 to 1 (renal vein renin activity from the involved or more severely effected side to renal vein renin activity from the contralateral side) is a reliable indicator of the functional significance of renal artery obstructive lesions and is correlated with the results of separated renal function studies. Comparison of the contralateral renal vein renin activity with the renin activity in the inferior vena cava allows demonstration of suppression of renin release by the contralateral kidney in patients with surgically correctable unilateral renovascular hypertension (because plasma renin activity from the low inferior vena cava is the same as plasma renin activity in arterial blood entering the kidney[27]).

Perhaps soon in general clinical use will be 1-sar-8-ala angiotensin II (P113 or Saralasin), a potent polypeptide competitive inhibitor of angiotensin II in instances of high endogenous levels of angiotensin, for example, as in renovascular hypertension. In settings in which endogenous angiotensin II does not have an active role, this analogue has been shown to be an angiotensin agonist, increasing blood pressure in normal subjects.[28, 2] Initial investigations indicate that, in sodium depleted patients, a short infusion of this analogue may enable the clinician to identify more rapidly and directly the patients who are likely to have renin dependent hypertension and who should undergo renal arteriography.

Management

Observations that progression is the usual clinical course of renovascular disease indicate that medical or surgical treatment of renal artery stenosis does not cure the disease but provides some amelioration of an active and progressive process.

When angiography demonstrates a characteristic lesion in a patient whose general health and life expectancy warrant consideration of surgical therapy, the functional significance and chances of surgical benefit are demonstrated by lateralization of the renal venous renin activity determinations.[3] Thus, in the patient with moderate or severe hypertension and functionally significant stenotic lesions, the treatment of choice is surgical. Indeed, in some instances when medical therapy alone has been pursued in patients with high grade stenosis, effective blood pressure control and hence decreased renal perfusion pressure has contributed to loss of renal function secondary to progressive ischemic atrophy and fibrosis of the kidney beyond the stenosis. Successful surgical treatment of the stenosis has arrested progression of atrophy and, in some patients, has improved renal size and function. However, the enthusiastic desire to remove renovascular obstructions surgically must be tempered by the need to evaluate carefully the associated disease in other parts of the body and by the frequency of significant lesions among normotensive patients.[31]



Fig. 3. Fibromuscular renal artery stenosis. Sequential studies revealing minimally changed appearances of renal artery angiographically but progressive renal atrophy of involved kidney. Surgical repair halted this progression.

Preservation of renal tissue has become the prime consideration in selecting therapy for renovascular hypertension because of the progressive nature of the disease on one hand and the frequently excellent response of blood pressure to rational medical therapy on the other.[3] In contrast to medical treatment, surgical therapy that involves successful revascularization by any of many procedures has the advantage of improvement or preservation of renal function along with the amelioration of hypertension. Nephrectomy should be considered only in patients with extensive renal atrophy and a poor response to an intensive medical program.

Results after 1 year of operative treatment of renovascular occlusive disease at 15 centers participating in the Cooperative Study of Renovascular Hypertension[13] sponsored by the National Heart Institute indicate that in the patient with functionally significant unilateral fibromuscular disease, 90 per cent benefitted from surgery and were classified as cured or improved. Of patients with bilateral disease, 76 per cent ultimately benefitted from surgery. Surgical procedures included vein bypass grafts, Dacron bypass grafts, thromboendarterectomy, autogenous arterial bypass, and nephrectomy. Of 26 patients who underwent corrective surgery with an anatomically successful result but who had no evidence of functional disparity by any of the diagnostic tests, only three were improved and 23 were failures. Other large series share this experience.[4, 11]

Operative results in patients with atheromatous disease indicate that, while results are not as favorable as they are in fibromuscular disease, largely because of associated atheromatous disease and its complications elsewhere in the body, the great majority of patients with functionally important stenoses are cured or improved; most series report 80 to 90 per cent of patients in these groups.[4, 13, 3] The surgical results of Ernst and co-workers[15] demonstrated this important point. In their group of patients with atheromatous disease localized to the renal artery, 87 per cent were classified as cured or improved and a 16 per cent operative mortality rate was noted. However, of the group with generalized disease, 53 per cent were cured or improved from surgery and the surgical mortality rate was increased to 31 per cent. Follow-up periods were 55 and 41 months, respectively, for the two groups.[3]

The series of reports by the Mayo Clinic group indicated that over a 7- to 14-year follow-up period, although blood pressure was controlled



Fig 3 cont d For legend see preceding pa e

medically the surgically treated patients bene fitted more both in long term relief of hyperten sion and in reduced mortality rate [18]

Over all the factors favoring a good surgical result are (1) youth (2) increased severity of hypertension and refractorinesss to medical treat ment (3) presence of fibromuscular disease rather than atheromatous disease (4) a functionally significant lesion and (5) the surgical possibility of repair specifically the surgical correction of associated aortic disease and the renal lesion during the same operation

The effect of long term medical management is revealed in the subsequent course of those hyper tensive patients with renovascular disease who do not undergo operative treatment for one or more of several reasons discordant arteriographic and renal functional data renovascular lesions in the absence of significant stenosis or hypertension the anatomic situation that technically would demand nephrectomy in the presence of a non atrophic kidney associated severe infirmities contraindicating surgery or personal preference for medical therapy Because of this selection process these patients do not serve as a control group to the surgically treated patients There is yet to be a true randomized prospective study However data obtained in this manner indicate that blood pressure generally can be controlled medically Nevertheless renal function can deteriorate in the presence of apparently adequately controlled blood pressure and the morbidity and mortality seem to increase over several years in the medically treated group[18] (Figs 3 and 4)

The goal of medical treatment of hypertensive patients with renovascular disease should be to normalize the blood pressure (diastolic pressure < 90 mm Hg) Comparison of data from surgical and treated groups indicates that the surgical group had a blood pressure level about 20 mm Hg lower than those treated medically Also the morbidity and mortality rate of target-organ damage from hypertension probably is reduced by normalization of the blood pressure and medical treatment that lowers the diastolic blood pressure to only 100 mm Hg probably is less effective

Hypertensive patients with normal renal func tion (serum creatinine level < 1 3 mg /dl) should follow a controlled sodium diet in the range of 60 to 90 mEq /24 hr as can be easily assessed by measuring 24 hour urine sodium excretion Some mild hypertensive patients may achieve normo tension with dietary sodium control alone but in most this will serve to expedite further pharma cologic antihypertensive therapy Moderate to severe hypertension may require multiple drug therapy and diuretics plus agents that interfere with renin release such as α methyldopa and propranolol are particularly useful [9]

In patients with loss of renal reserve several additional factors must be considered Drug



Fig 4 Atheromatous renal artery stenosis *A* Excretory urogram at time of hypertensive evaluation *B* Repeat urogram 1 year later while blood pressure was controlled on medical program *C* Angiogram obtained at that time revealing typical atherosclerotic involvement of aorta and renal arteries (both segmental and orificial stenoses)

therapy may frequently provide unwanted side effects in such patients diuretics (such as the thiazides) may cause depletion of body potassium stores, hyperglycemia, and elevation of serum urate, which may progress to clinical gout Therefore a combination of dietary sodium restriction and nonkaliuretic diuretic agents may be useful but caution is required because when the serum creatinine level exceeds 4 0 mg /dl the possibility of serious hyperkalemia exists

With more severe loss of renal function (serum creatinine level > 6 0 mg /dl in women and > 8 0 mg /dl in men), diuretics may cause depletion of body sodium and extracellular fluid volume with consequent further reduction of renal function When this occurs nondiuretic conservative management of renal failure and nondiuretic pharmacologic treatment for hypertension may be indicated The intermittent administration of loop diuretics in combination with vasodilator antihypertensive medications such as hydralazine or minoxidil[3] is useful in patients with hypertension and renal failure who do not respond to more conservative measures If the renal failure or hypertension cannot be managed by these modalities, dialysis or transplantation should be considered

Because of the observed clinical course all patients whether surgically or medically treated require close continued observation after the initial management Quantitative assessment of renal function by standard clearance techniques and by isotope renography should be performed at least yearly Additionally comparison of follow up yearly roentgenograms of the kidneys with tomography gives important information regarding renal size If renal mass is reduced or if renal function is diminishing suggesting infarction or ischemic atrophy arteriography should be repeated in order to reassess the original lesion or the current integrity of the surgical repair Additionally extrarenal arterial involvement by fibromuscular or atheromatous disease may become symptomatic

Current evidence justifies the vigorous approach to the management of severe renal artery stenosis and resultant moderate and severe renovascular hypertension by surgical means Evidence is lacking for the use of this approach in the patient with less severe renovascular disease If in less severe renovascular disease medical management maintains normal blood pressure and if on reevaluation there is no reduction in renal function the continuation of such medical management is justified If renal function is diminishing or blood pressure has not been controlled at reassessment then the aims of treatment, namely preservation of renal function and prevention of the morbid events resulting from uncontrolled hypertension have not been met and surgical therapy should be considered after appropriate investigations

Summary

Renal artery stenosis either fibromuscular or atheromatous is probably the most common cause of secondary hypertension in man Both of these diseases are active ongoing processes that may be ameliorated but not cured by medical or surgical treatment

The clinical history and examination of the patient with hypertension may help differentiate renovascular hypertension from essential hyper tension The presence of a systolic–diastolic or continuous bruit is often an indicator of severe renal artery stenosis

Systemic hypertension is the physiologic conse quence of significant renal artery stenosis Knowledge of the basic concepts of the renin–an giotensin–aldosterone system as has evolved from experimental models of renovascular hyper tension forms the basis for understanding the process of evaluation and treatment of such patients

The treatment of choice for the patient with severe hypertension and a functionally significant renovascular lesion is surgical—both in terms of successful treatment of hypertension and im proved long term prognosis Diligent periodic reevaluation of these patients as well as those with less severe hypertension who are receiving medical treatment enables the physician to select the proper management that offers optimal control of patient blood pressure and avoids target–organ damage to the kidneys central nervous system or cardiovascular system

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Cardiac pacing and pacemakers VIII The pacemaker follow up clinic

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The function of pacemaker systems has always been variable and patients with implanted pace makers have had intercurrent events which affect the interaction of the pacemaker system and the patient Patient welfare has required continued observation to reduce the incidence of sudden and unpredicted pacemaker system failure to detect substandard performance of some units and to produce maximum longevity of those units capable of prolonged operation It should be remembered that for the patient s safety all fail ures to pace are equivalent whether lead displacement or fracture electronic failure or power source depletion

Pacemaker failure

Until recently the average longevity of implanted pulse generators was short and the pread of failure wide so that adequate follow up involving office or clinic visit was not feasible for large numbers of patients A high incidence of undetected failure and a short maximum longev ity occurred if units were removed electively at some specific period such as at the 10 per cent or 50 per cent failure time The alternative was to follow the implanted pacemaker carefully with periodic clinic and telephone transmission

The availability of lithium rather than mercu ry-zinc cells has caused a substantial change in the behavior of implanted pulse generators and consequently the failure patterns which must be detected (Fig 1)

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The failure pattern of mercury-zinc cell pulse generators implanted since 1969 established an effective longevity range of 18 to 36 months with the initial failure appearing within the first three months after implant 10 per cent by the fifteenth month and enough failures appearing thereafter to require the onset of monitoring early after implant During 1976 the average pulse generator longevity for battery depletion for those genera tors removed during that year was 35 8 months but *electronic* failures occurred as well so that the average longevity of failed generators (for all causes) was 33 4 months The standard deviation of the mean was 10 7 months so that ±2 S D extended from 12 months after implant until 45 months after implant[1] (Fig 2)

These were pulse generator failures only and do *not relate* to over all system failure which includes a substantial portion of electrode and other malfunction [2] Even with lithium cell pacemakers all secondary interventions bring the total reexploration rate to 20 per cent 3½ years after implant

Review of a transtelephone monitor service *in the general population* showed that *electrode* problems occurred in 9 5 per cent of all implants and 10 per cent of all failures were reported during the initial telephone contact *whenever* that occurred after implant so that a substantial *number of* patients had no cardiac control at all *for an unknown period after* implant and before the initial contact

More *recently* there were 340 pacer system malfunctions out of 1 705 followed via telephone over a four year period *Nine and* seven tenths per cent of all system failures occurred within one week of implant 41 per cent were caused by battery exhaustion and 59 per cent were of other

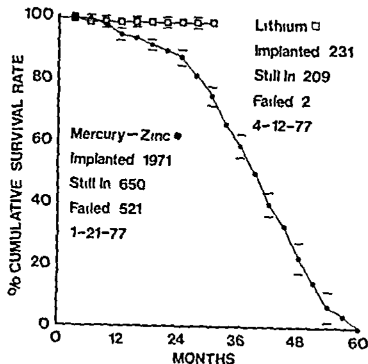


Fig 1 Simultaneous cumulative survival data for all mercury-zinc pulse generators used since 1969 and lithium powered pulse generators since 1974 at Montefiore Hospital and Medical Center shows a distinct difference in longevity experience With such different failure patterns different follow up is required

causes Five per cent were deemed to be related to electronic component failure and four per cent to arrhythmias which were not pacer related Fifty per cent of all failures were caused by lead distraction high threshold poor sensing or fracture None of these failures are affected by longevity of the power source[9] It is even possible (though undemonstrated) that with greater longevity power sources these problems will occupy an even greater number as well as proportion of all failures

During analysis of 1 873 pulse generators implanted during an F D A sponsored registry * from July 1974 to December 1976 88 (4 7 per cent) failed thirteen for early battery exhaustion and 74 for component failure with one unit having both component and battery failure Lead failure occurred in 98 (11 6 per cent) patients of 844 initial implants Electrode malposition was concentrated during the first post implant days but fracture erosion infection and high threshold arose late after implant as well as early[10]

The three sets of data indicate that problems of cardiac pacemaker implantation have not been fully resolved All data which does exist indicates that pulse generator longevity can be increased by careful follow up and that electrode problems remain to be detected by follow up

Implanted pacemaker recall (which implies failure of some aspect of initial design) has become a common event for the mercury-zinc pacemaker Since the introduction of lithium cell units, two models[11, 1] have been recalled With newer circuitry and complexity, it is likely that other models will fail to operate satisfactorily

The original pacemaker clinics were founded by early workers who followed their patients at a time when interest in the fate of the individual patient and the implanted or external pacemaker was intense[13] To x ray clinical observation and electrocardiogram a powerful tool was added analysis of the pulse generator artifact for deviation from normal function[14, 15] The electronic clinic thus used facilities specifically suited to pacemakers Subsequently as patients became more numerous statistical capability was added so that over all patient and pacer longevity could be ascertained[16]

All pacemaker follow up systems should meet the following goals

1 Prediction of impending pacemaker system failure before the patient is at risk

2 The capability of ascertaining the nature of the malfunction when failure is about to occur or has occurred

3 Recording of patient location should a pattern of systematic pulse generator failure develop or recall occur and

4 The development of statistical data specific for one clinic or part of a much larger data base

The electronic clinic which involves a direct patient visit analyzes the pacemaker stimulus wave form and provides several unique abilities

1 Evaluation of renewed symptoms despite apparently normal pacing Though such evaluation may require the maximum operator and electronic skill analysis of the stimulus artifact is the best analysis of electrode disruption available[17] It surpasses x ray in detection of partial lead fracture and can be diagnostic of insulation disruption when no x ray findings exist

2 Adjustment and evaluation of programmable pacemakers a factor likely to become a more important aspect of pacemaker management

3 The early post implant observation for stability of sensing and pacing wound stability

* Food and Drug Administration Contract No 223 74 5199

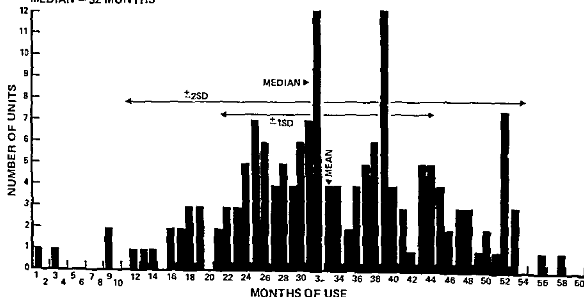


Fig 2 Pulse generators removed for electronic failure or battery depletion during 1976 approximated a normal distribution of longevity with a mean at 33 4 months and a standard deviation of 10 8 months

and the appropriateness of the pacing rhythm for the patient

Organization of a pacemaker clinic

I Patients should be seen on a consistent schedule and not seen solely with the return of symptoms The schedule should be based initially on the stability of the electrode so that patients are seen early after implant of a new electrode and pulse generator and need not be seen early after pulse generator replacement

II Pacer records should be kept separate from the hospital record system records should be immediately retrievable and should contain (1) patient data i e name age identification number address and phone number (2) pacemaker data i e model and serial number and records of rate electrocardiograms and other parameters of function

III Patients should be subjected to

1 X rays once a year or for children every six months to note for electrode position

2 Twelve lead electrocardiogram at each visit pacing and with the pacer inhibited

3 A long rhythm strip in the free running and magnet modes

4 Display and recording of the pulse generator stimulus in the free running and magnetic modes and representative programmed functions[1]

5 Programming of the programmable pacemakers through a variety of its functions with recordings of representative wave forms rates and other programmable factors

6 Evaluation of the implant wound

7 Measurement and recording of the pacemaker rate in the free running and magnet modes

Measured factors

I Rate From the initial pacer designs rate was meant to be a stable element of pacer function Rate was an indicator of battery depletion and runaway to rates of 200 to 600 per minute with serious and even fatal consequences occurred [9, 11] Rate decline later became the universal indicator of power source depletion as it remains today Until major rate change occurs a variety of patterns can occur which require interpretation

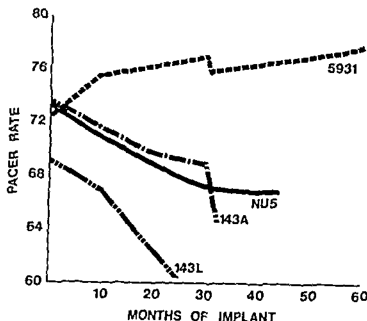


Fig 3 Four common patterns of rate evolution The 5931 shows a progressive increase not beyond the physiologic range The NU5 decline a pattern of minor electronic malfunction reached a stable plateau 30 months after implant The 143A generator declined slowly and then rapidly with battery depletion The 143L generator showed progressive rate decline immediately following implant though this did not result from battery depletion When the rate became less than physiologic the generator was removed

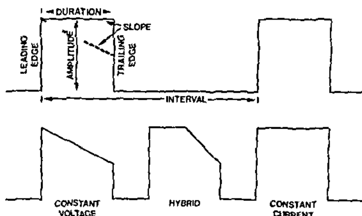


Fig 4 Analysis of a pulse generator impulse is based on analysis of various aspects of its shape duration and interval between pulses Several typical normal patterns are illustrated The impulse need not be a square the relationship of the height and width are functions of the display scale factors

A Rate drift If a progressive constant rate decline occurs the pacer rate may reach a permanent plateau or rate may decline to non physiologic levels As small or moderate declines are physiologically well tolerated these can be observed and evaluated If the plateau occurs at a physiologic level no action need be taken If continuing decline occurs, generator replacement is required (Fig 3) An upward rate drift is more ominous especially if coupled with an accelerating rate of increase, though here, too the rate of increase and the relation of the rate to the physiologic is important

B Rate instability Variation of rate about the nominal is usually interpreted as instability of the electronic circuit Nevertheless, each instance must be individually evaluated Small variations may be recurrent and stable over a prolonged period and be physiologically inconsequential Lithium cell output voltage is much more sensitive to change in ambient body temperature than mercury zinc so that rate variations with fever are to be anticipated Nonetheless, all rate instabilities bear observation

II Pacemaker output Pacer output has been readily calculable in a variety of units over a number of years Two patterns have evolved those units in which threshold can be determined as a percentage of total pacemaker output but the stable output is fixed at maximum two presently available versions are the Vitatron and Elema* Vario pacemakers [1] The second pattern is that of programmable output reduction either by shortening the pulse duration as in the Medtronic† 5961 and CPI‡ Microlith P programmable pacers, or reduction of output voltage as in the Cordis Omnicor [4]

The two systems provide a check on threshold which can be important in the occasional problematic implant Both systems allow the possibility of the evaluation of impending difficulty, though the latter provides the ability to provide higher outputs when necessary or reduce output substantially to increase pacer longevity if that is suitable Though long term electrode threshold is substantially stable (*see* Cardiac Pacing and Pacemakers IV) variations can occur Electrodes may be displaced from the cardiac apex or the myocardium early or late The first indication and the key to its assessment is the threshold of stimulation In the unusual instance that threshold is above conventional pacer output it is possible to increase the output of some programmable pacers continue pacing consuming only a portion of the pacer longevity

During follow up of a difficult pacemaker implant or revision of a failed procedure it is

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desirable to implant a unit with a programmable output to evaluate the constancy of the new threshold increase pulse generator output as necessary and decrease output when constant threshold occurs and allow greater generator longevity A clinic with such capability is invaluable under these circumstances (*see* Cardiac Pacing and Pacemakers VI)

Stimulus artifact The stimulus artifact is the emission of the pacer output circuit through the load i e the tissue portion of the circuit and the electrode A variety of changes can be found in six factors which can be displayed on the oscilloscope photographed analyzed and recorded (Fig 4)

The six factors are

1 The *shape* of the leading edge
2 The *shape* of the trailing edge
3 The *shape* of the slope

As the impedance of the tissue increases during the passage of the impulse the current delivered tends to decrease In the case of a *constant voltage generator* the impedance change will be a substantial portion of the total output impedance and the flow will decrease so that a *slope* will be present from leading to trailing edge In a *constant current generator* the output impedance of the generator is sufficiently high that the impedance change never becomes a substantial portion of the total and the flow may not change perceptibly No slope may then exist An intermediate current flow with an initial plateau and then a slope can exist with an output impedance between constant current and constant voltage Once implanted the output artifact measured shortly thereafter will approximate the normal for that generator and electrode system and should be recorded for future reference

Should the impedance of the system increase the constant current artifact will tend toward the constant current shape i e the slope will decrease This change can be found with a partial lead or connector break with the lead insulation intact Should the impedance decrease distortion of the generator wave form will occur Decreased impedance occurs during insulation break with or without fracture of the wire The vector of current flow change can be detected on the oscilloscope or the vector cardiogram Lead disruption with increased or decreased impedance is readily recognized by artifact change whether or not pacing or sensing has been affected and

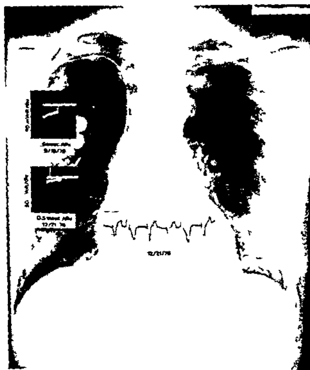


Fig 5 Patient seen with normal pacing and sensing but with a marked change in stimulus amplitude and configuration indicative of a lead fracture borne out on x ray

when normal artifact distortion may be the first and only indication of difficulty before actual pacing failure occurs (Fig 5)

4 *Amplitude* of the over all impulse may be measured at leading or trailing edge or between In the past when pulse durations of up to 2 0 msec duration were in use the measurement frequently was done 0 5 msec into the pulse[4] Presently the most common impulse duration is 0 5 msec Measurement of the over all amplitude is affected by phase of respiration the patient s position i e sitting or lying and the movement of the heart within the chest with respiration Amplitude *alone* is only a suggestive indicator of change in pacer output

5 The *impulse duration* does not usually change with malfunction of the pulse generator load as that is fixed in the generator output circuit It *can* change (a) if it is a programmable function and may have been spontaneously reprogrammed[5] (b) it may have been inadvertently reprogrammed (or without the knowledge of the pacer clinic) (c) a change may have occurred in the generator output circuit (d) as increase in pulse duration has been made an accompaniment and indicator of power source

CARDIAC PACEMAKER CENTER
MONTEFIORE HOSPITAL & MEDICAL CENTER BRONX N.Y. 10467 • (212) 920-4481

MILLISECONDS (msec) /division 0.5

DATE 052777

NAME

[redacted]

PACEMAKER [redacted]

[redacted] 7/31/71

ELECTRODE
MEDT-6917-35 - A052370

MONTHS USE ELECTRODE 26 PACER 26

NON TRIGGERED/ASYNCHRONOUS RATE 71.7

MAGNETIC RATE 71.0 /min

PACEMAKER IMPULSE
POLARITY UNIPOLAR LEAD II
MILLIVOLTS (mV) /division 20

L-70
PULSE DURATION 1.4 msec PLATEAU 1.4 msec MAXIMUM AMPLITUDE 44 mV

REPRESENTATIVE RHYTHM STRIP LEAD II

THRESHOLD BELOW T-100

UNDERLYING RHYTHM	TRIGGERED RESPONSE	MAGNETIC RESPONSE	WOUND
PROBABLE JUNCTIONAL RHYTHM	NORMAL	NORMAL	HEALED

INTERPRETATION V-INHIBITED (VVI) PACER ENTIRELY IN FIXED MODE.
SENSING ABILITY CONFIRMED BY INHIBITION BY EXTERNAL TRIGGER - NORMAL FUNCTION

THANK YOU FOR THE COURTESY OF THIS REFERRAL. DATE NEXT VISIT 092677

J. W. Escher M.D. Seymour Furman M.D. J. Fisher M.D.

Fig 6 A typical data sheet for a patient visit Included are oscilloscopic display of the stimulus artifact and scale factors patient identification data including name age insurance data address telephone number and nearest relative pacemaker identification data including model and serial number date of first pacing and date of implant of the present pulse generator and the age of the generator electrode identification data including manufacturer model and serial number a typical electrocardiogram and if the pacer is not inhibited by spontaneous cardiac activity external triggering to demonstrate continued sensitivity and the underlying paced rhythm (additional artifacts—center)

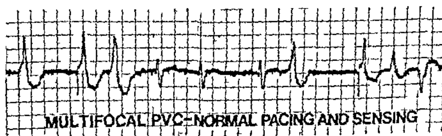


Fig 7 Telephone transmission showing normal pacing and sensing and as well multifocal premature ventricular contractions

depletion (along with rate change) it will occur as the battery (or cell) voltage decreases (*see* Cardiac Pacing and Pacemakers VI Fig 8)

6 The *impulse interval* is the reciprocal of the generator rate and decreases (rarely increases) as an indicator of battery depletion

The electrocardiogram should be used to check pacing and sensing function Whether or not sensing is shown to be normal on ECG the pacer should be driven by stimulation with an external pacer (chest wall stimulation)[2] via the intact skin to determine its response refractory period if necessary and the presence of partial recycling[28] should that be present (Fig 6)

Once all measurements are completed it is very likely that an adequate determination can be made of the state of pacemaker function and the nature of the malfunction if any

Transtelephone monitoring

There are 150 000 to 200 000 patients in the U.S.A with implanted cardiac pacemakers It is impossible for all to be observed as outpatients on a schedule sufficiently comprehensive to detect all or even most of these failures Several of the most important determinations in pacer follow up i e the ECG the rate in free running and magnet mode and in part the stimulus artifact can be converted into tones which can be transmitted via telephone decoded and reconstructed to indicate the state of pacemaker function As telephone service is ubiquitous in the U S A patients can be monitored as frequently as necessary with minimal dislocation and can be brought into the clinic only if uncertainty exists if x ray or more exacting electronic analysis is required or if intervention is indicated In areas where no pacemaker clinic exists transtelephone monitoring is a satisfactory replacement where a clinic does exist telephone monitoring is part of the technique

Purposes of transtelephone monitoring

1 Careful follow up to provide maximum patient safety and longevity of the pacing system

2 Careful observation of pulse generator series which are suspect on a recall list or are beginning to show early and as yet indistinct signs of malfunction

3 ECG monitoring for an intercurrent arrhythmia

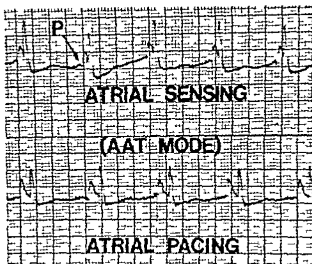


Fig 8 Normal pacing and sensing seen on an ECG transmitted by telephone The pacing mode is atrial triggered so that stimuli follow the P wave during normal sensing (*above*) and produce P waves (*below*)

4 Follow up as a laboratory resource for the physician who makes the decision concerning his patient

5 Extension of pacer follow up to areas remote from a pacemaker clinic and for patients unable to travel

Varieties of transtelephone monitoring

Rate Only Initially monitoring was rate only no indicator of ventricular capture existed It depended for effectiveness on the presumption that a pacer impulse consistently provided ventricular capture once an electrode was demonstrably stable In only one instance did an error occur in which stimuli did not produce a ventricular response Nevertheless this approach is now obsolete[3]

Rate and non ECG indicator of ventricular capture Two varieties of non electrocardiographic indicator of ventricular capture exist

1 Rate and digital plethysmography was adapted from the rate only technique because of the occasional need to determine whether ventricular capture had occurred This technique is somewhat better than rate only but almost certainly allows false positive and negative interpretations which have never been reported[31]

2 Rate with detection and discrimination of pacing and tracking pulses which are used in two different pulse generators[32] There is no specific indicator of ventricular capture by the stimulus

Table I Telephone monitoring schedule

Months in 1972		*Months in 1975*	
1 6	Q 2 Mo	1	Weekly
7 15	Q 1 Mo	2 18	Q 2 Mo
16 17	Q 2 Wk	19 24	Q 1 Mo
18	Weekly	24 30	Q 2 Wk
		30	Weekly

Table II Transtelephone monitoring 1 191 patients—(10/13/69 to 1/31/77)

Failures detected	524
Errors (TTM—rate only)	3
Loss of pacing (IAIT)	8
Lead fracture	16
Dead (pacer O K)	163
Elective end of TTM	151
Presently active	326

A spontaneous beat has a shorter duration tracking pulse into it which the telephone monitor can distinguish It is assumed that the tracking pulse responds to spontaneous beats but this is not certain

Rate and electrocardiogram

This approach is widely used provides the pacemaker rate during the free running and magnet modes and a simultaneously transmitted electrocardiogram to confirm capture and sensing This technique provides an electrocardiogram which is universally understood as an indicator of cardiac activity The device is sufficiently simple so that individual patients can readily use it at home [11]

Rate electrocardiogram and electronic analysis

This is the most sophisticated system of data transmission and provides the greatest amount of data As the technique and transmitter are complex the patient must travel to the transducer (perhaps in a physician s office) from which data is transmitted to a central facility

Electrocardiography in transtelephone monitoring

The ECG monitors provide data and pacer stimuli similar to that of conventional electrocardiography and indicate failure to sense, pace or both as well as clear cut indication of normal function (Fig 7)

Perhaps the most serious artifact is that caused by the single ECG lead, one in which electrodes are placed on both limbs The stimulus or the QRS complex may be isoelectric or indistinct Telephone line noise movement artifacts and electrical transients may occur as well as 60 Hz interference If the pacemaker rate in the magnetic mode must be determined the patient places the magnet over the pulse generator (Fig 8) If a tremor is present it will be transmitted to the ECG and if the patient cannot accurately place the magnet, an incorrect rate may be found The induction of a competitive pacemaker rhythm is benign Intercurrent findings may include premature ventricular contractions runs of ventricular tachycardia the presence of atrial fibrillation etc

The monitoring schedule

The schedule should conform as much as possible to the anticipated failure pattern of the generator and the lead system Where a pulse generator system in newly available and no clear cut pattern is known a decision can be made to monitor according to a previous projection If the unit is known to be in danger of premature power source depletion or electronic failure more frequent monitoring can be undertaken

The two dominant power sources the mercury zinc battery [6] which is still used and useful *for* short duration application (3 to 4 years) and *the* variety of lithium based cells[1] for *smaller or* longer lasting generators should be *monitored* weekly after implant for one month to *detect* electrode failure If the electrode remains stable less frequent monitoring can begin For the mercury—zinc cell pulse generator weekly *monitoring is* begun at 30 months in anticipation of the *steep* rate decline accompanying battery depletion For the lithium based power *source* which shows a progressive rather than a *sudden* decline monitoring monthly begins at *30 months* (Table *I*)

Results

Only three errors have been made by our program two with rate only monitoring with a normal rate but without consistent capture in *one* and in another *rate* was stable and ventricular capture *consistent during* each transmission As battery voltage had declined between transmissions *intermittent* pacing and asystole were demonstrated on subsequent direct examination

The error rate for transtelephone monitoring is thus 3 out of 524 patients followed to pulse generator replacement or 0 56 per cent

Of 1 191 patients followed since October, 1969 failure was detected in 524 sudden loss of pacing after a satisfactory transmission in 8 and lead fracture in 16 Death occurred in 163 though in none was it related to pacer malfunction Despite careful follow up 151 patients terminated monitoring the majority for vacation travel not to be interrupted a few others because they tired of consistent monitoring and others at the election of the pacer staff The last group were pacers in a careful observation of recall status in which we had decided that sudden *electronic failure* might occur between calls

The total error and undetected cessation of pacing rate (for all causes) for transtelephone monitoring is 5 per cent (27 of 524) for patients followed to generator replacement If the calculation is of *all* patients monitored assuming no deaths were pacer related then it is 2 3 per cent (27 of 1 191) (Table II) In either event it provides far *greater safety* than can be achieved by any other system

If we assume that most lead fractures are sudden events which ECG and rate cannot detect in advance (an assumption which is almost certainly correct) then the failures are 11 of 1 191 or 0 9 per cent

Because of the ability of transtelephone monitoring to provide careful widespread follow up readily performed by technical staff supporting the cardiologist *and surgeon* its utility remains great Such follow up allows development of an accurate data base concerning pacemaker function It should be extended to include additional patients but the call schedule must *reflect* the power source in the pacer being followed It is inappropriate to test a lithium powered pacer as if it were powered by a mercury–zinc battery Once this is accomplished appropriate utilization is achieved

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Viruses in Balkan nephritis

That Balkan nephritis (BN)—a familial slowly progressive degenerative disorder of the kidneys—might be of viral etiology was not suspected until Georgescu and colleagues demonstrated by electron microscopy the presence of reovituslike particles in renal parenchymal cells of patients dying of this condition. The round particles observed in the cytoplasm of tubular epithelial cells varied in size from 50 to 90 nm and exhibited an electron-dense central core, surrounded by a distinct peripheral layer. Formerly clinical and laboratory findings failed to suggest an infectious etiology. The afebrile clinical course (except for intercurrent or terminal infection) the lack of a regularly antecedent illness and of typical pathological reactions spoke against infection.

Encouraged by this preliminary evidence we initiated a systematic search for hidden viruses in the kidneys of BN patients. In the last several years an increasing number of viruses have been found to be carried in the urine of man. However we succeeded to recover only an adenovirus strain from the urines of clinically confirmed BN patients and there was circumstantial evidence that this strain was an accidental passenger virus with no relationship to the patient's illness at the time of demise. Our attempts at uncovering latent viruses by cell cultivation have been handicapped by lack of satisfactory virus harboring tissue. We were not successful in propagating autopsy material and biopunctures often failed to provide renal tissue because of the advanced atrophy and sclerosis of this organ. Moreover fragments were frequently obtained from fibrous connective tissue rather than from the renal parenchyma, and resulted in monolayers of fibroblast type cells in culture. However long term organ cultures and co-cultivation of kidney fragments and trypsin-dispersed human embryo kidney cells also yielded negative results and it became thus apparent that the major obstacle in isolating the involved agent consisted in the fastidious difficult nature of the virus. On the other hand we have recovered several cytopathic agents from throat swabs and urine specimens of family members sharing the housing and living conditions of BN patients. Some of these agents could readily be identified as adenovirus or echovirus strains, whereas other isolates still await identification.

Current epidemiologic data with the highest incidence of BN in women of the childbearing age suggested that a vertically transmitted agent of low grade infectivity might be involved. With maternal infection progressing during pregnancy the fetus may become chronically infected and this infection may persist through birth and for a variable period afterward. Serological diagnosis of intrauterine infections is based on the fact that the fetus can respond immunologically already from the twentieth week of gestation. As IgA and IgM antibodies are not transferred from the mother their presence in the cord blood indicates a fetal response to a prenatal antigenic stimulus. We used the immunodiffusion method to test this possibility by screening sera of newborns from the endemic and a control area for raised IgA and IgM levels suggestive of intrauterine infection. The non specificity of this method rendered it suitable for checking infections of unknown etiology. However this study did not disclose any statistically significant difference of the incidence of infection in the endemic and the control area.

The assumption that BN might be a late post infectious phenomenon or a chronic state of childhood illness was hardly tenable since we could establish no regularly antecedent disease. The contention that the antecedent infection might be inapparent was disturbingly difficult to investigate and could only be tested sero-epidemiologically. The hypothesis implied that all viruses are suspected which are able to cause mild or inapparent but persistent infection in children. However sera from 35 patients with BN, 35 cases of lupus nephritis and 105 selected healthy controls matched for age, sex and residence yielded no consistent pattern of antibody to echovirus and adenovirus, *herpes virus hominis* Types 1 and 2, ground squirrel herpes virus, human, murine and ground squirrel cytomegalovirus, mumps, respiratory syncytial, parainfluenza, influenza A and B, sindbis, west Nile, hypr, tribeč and reovirus antigens.

The existence of natural foci of viral infection in areas endemic of BN would afford an attractive explanation for the very restricted geographical distribution of this disease. Epidemiological search for possible natural foci led to the isolation, identification and characterization of a tribeč type arbovirus strain from *Haemaphysalis punctata* ticks, of several novel cytomegaloviruses from wild mice of the *Mus musculus* and *Microtus arvalis* genera, and from the ground squirrel (*Citellus citellus*) as well as to the recovery of a ground squirrel herpes virus. All these viruses had features which appeared relevant to the implication of viruses in renal disease. The tribeč like arbovirus induced in mice focal degenerative lesions in the tubular segment of the nephron. Cytomegalovirus of *Mus musculus* mice caused glomerulonephritis and was found to be under genetic control of the natural host etc. Nevertheless, none of these viruses shared morphological and/or biological features of the viruslike particles seen by electron microscopy and there was no evidence to link any of them with the etiology of BN.

In spite of the fact that our studies failed to elicit a recoverable virus from the kidneys of BN patients and that

the influence on the carrier host of the reoviruslike agent is not yet understood the possibility of an infectious etiology of BN was further supported by the demonstration of virus like particles in renal biopsy specimens of three further BN patients as well as by the findings of Apostolov and colleagues who lately described corona virus particles in the cytoplasm of renal cells obtained by biopsy from patients with clinically confirmed BN (corona viruses have previously been named reo like reovirus like or difficult viruses etc) Since no *in vitro* serologic procedure has been developed as a useful diagnostic tool in this disease and the involved virus has not been cultivated in tissue culture or laboratory hosts little is known of the nature of this agent Repetition of such attempts and extension of the studies to embrace most of the modern techniques of virology are prerequisite to any progress in this field Meanwhile evidence of viral etiology in BN is still entirely morphological

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Marked decline in serum digoxin concentrations during an episode of severe diarrhea*

During the past several years numerous studies involving digoxin pharmacokinetics and bioavailability have been reported However relatively few studies have been directed to the actual mechanism of digoxin absorption and in particular to the influence of factors such as altered intestinal motility and transit time intestinal disease and the role of the enterohepatic circulation From these studies it does seem apparent that disturbances of normal gastrointestinal function might well result in a significant alteration of digoxin bioavailability We would like to report such a circumstance involving an individual who demonstrated profound differences in serum digoxin levels during an acute transient diarrheal illness

A 24 year old healthy male volunteer received four 0 25 mg digoxin tablets (Lanoxin Burroughs Welcome Lot 022 1) as part of a more extensive study of digoxin absorption and pharmacokinetics Three hours after ingesting the drug the patient developed repeated episodes of watery diarrhea which persisted throughout the subsequent 24 hours A total of 15 serial blood samples were drawn during the first 24 hours following which a single blood sample was obtained every 24 hours for three days Six weeks following this illness the patient was restudied in a healthy state using the same protocol with tablets from the same lot The serum digoxin concentrations were determined in duplicate using an I radioimmunoassay (Schwarz/Mann) with the subject s digoxin free control plasma serving as the blank for the standard curve done simultaneously with experimental samples The resultant serum levels were plotted against time for both treatments (Fig 1) Since the patient was involved in a larger study which involved intravenous administration of 1 mg of digoxin it was possible to calculate the absolute bioavailability of the tablets by the area under the curve method Although the time to reach peak serum levels did not differ and the peak levels were similar the calculated absolute bioavailability of the tablets given when the patient developed diarrhea (16 per cent) was substantially less than when the drug was administered under normal circumstances (84 per cent)

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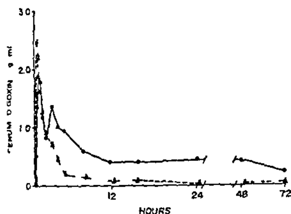


Fig 1 Graph showing serum digoxin concentration versus time *The solid line with circles* represents the normal clinical state *The broken line with triangles* indicates the diarrhea state Note that the initial peak serum concentrations are similar however the drug is rapidly eliminated from the body with the onset of diarrhea

Despite the fact that this study involved only a single dose of digoxin we feel that the magnitude of the observed effect suggests that diarrhea may be of clinical importance in patients taking digoxin on a chronic basis Although the mechanism responsible for such a dramatic alteration of serum digoxin levels cannot be established from the study it was clearly not a result of vomiting or of incomplete ingestion of the tablets Since the peak serum levels and peak times did not appreciably differ in the two studies the initial absorption of digoxin prior to the development of diarrhea was probably normal The pronounced difference following onset of diarrhea is suggestive of a profound increase in fecal elimination of the drug Mechanisms which could explain these observed differences include more rapid elimination of undissolved drug from the gastrointestinal tract altered intestinal permeability increased secretion of digoxin into the gastrointestinal tract and interruption of the enterohepatic circulation

We report this observation to call attention to the fact that acute diarrhea appeared to have a marked influence upon serum digoxin levels and to point out the need for further studies to more fully elucidate the effects of gastrointestinal disturbances on digoxin elimination particularly in the chronically digitalized patient If confirmed by more extensive studies this finding may prove to be of clinical importance when severe diarrhea supervenes in such patients

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Survival curves applied to acute myocardial infarction

In some 50 per cent of cases depending upon the criteria a recognizable acute myocardial infarction is fatal in the first few weeks, although it may still contribute to death ultimately

It is the possibility of preventing short term deaths which is the chief justification for intensive care and resuscitation procedures. Arising out of this has been an increased attention to numbers dying, or surviving as a function of the time elapsing since the onset of acute symptoms.

Short term death is not always instantaneous but occurs at

a steadily diminishing frequency over a period of weeks References to a high early mortality are too numerous to list and the use of time units of varying ratios—minutes *hours days and weeks—over the period of mortality has* probably been one factor helping to obscure the fact that the survival curve is a smooth one A second factor is the need for a study population of many hundreds of thousands Only a few population studies in the United Kingdom have been on a scale sufficient to generate a recognizable curve[3] Generally the mass of published data has been concerned with survival of those patients coming into medical care When the deaths occurring in the same population before or without arrival of a physician are also counted—usually by a calculation involving multiple assumptions—then the two survival curves are seen to be wholly different[3] The true curve can be *appreciated to lie in between that of unattended deaths* and that of hospital fatalities which are predominantly early and late respectively

The inverse exponential character of the survival curve (numbers surviving plotted against time) becomes clear when the appropriate variable is transformed by using a logarithmic scale That the curve becomes straight if the time axis is chosen was demonstrated by Fulton and colleagues in relation to cumulative mortality the converse of survival and by Tunstall Pedoe[7] using his own data[6] This was in accordance with other reports on infarction series [ ] where the authors had chosen coincidentally to transform the scale on the time axis by similar spacing of minutes days and weeks Transformation on the other axis can be seen in the considerable literature on the subject of survival curves as applied to life tables to mechanical components in industry [ ] to follow up of cancer and to groups of experimental animals following exposure to irradiation Such survival curves have been found to follow a Gompertz Makeham a Weibull or a multiple logistic function Curve fitting is not a mere academic exercise but facilitates study of the pathophysiologic mechanisms some such as autonomic nervous imbalance potentially modifiable

An exponential Weibull distribution is preferred by Saracci to the exponential distribution per se since the latter implies that the rate of mortality stays constant with time whereas the rate or force of mortality starts off high and subsequently decreases somewhat when this is plotted as a function of time the so called Hazard Curve as opposed to the Survival Curve although the same data are used The numbers of temporary (less than 4 weeks) survivors do follow a simple negative exponential curve however and the writers found a coefficient of correlation within 1 per cent of unity for either sex within two series of 1 858 subjects and 998 subjects respectively

Change from a high initial mortality to a lower one later has also been described as a Negative Aging Effect in considering the life of industrial components or a Type B Curve in radiobiology When the later mortality increases then Positive Aging or a Type C survival curve showing a shoulder may become *evident Whether described graphically or by* fitting equations the distortions of survival curves which result from active interventions will require the same kind of attention as one would devote to percentage increase of survivors in a more simple situation

In the meantime and for many purposes thereafter the exponential model is probably sufficiently accurate to allow us to quote the median duration of temporary survival This the time by which 50 per cent of the short term mortality has occurred and its degree can take the place of mortalities at for instance 24 hours 7 days and 48 days The mix of early and late rescue cases may be invalidating much present assessment of exacerbating factors and of preventive or corrective measures

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Of Ewart's sign and myocardial infarction

The term Ewart's sign was introduced to indicate a cluster of crepitant rales posterior to a large heart and produced by compression atelectasis. But it is interesting that the lungs posterior to the heart often reveal crepitant rales shortly after the onset of myocardial infarction or in association with acute coronary insufficiency even in the absence of cardiac enlargement. These rales slowly subside and disappear in a few hours to 2 or 3 days The precise mechanism of these rales is certainly not clear It may be a mild form of cardiac causalgia (causalgia minor) These rales are often not noted by the physician unless he carefully examines his patient Left ventricular congestive heart failure alone cannot be responsible for the sharply localized cluster of râles. Congestive failure of the acutely damaged or ischemic left ventricle may be a contributing factor However if congestive failure of the left ventricle were entirely responsible for this finding the rales would not necessarily be sharply located only posterior to the heart I would postulate that the major factor responsible for these râles originates from the heart itself by mechanisms that produce reflex vasoconstriction of the small pulmonary vessels i.e arterioles and veins, with the accumulation of small amounts of intra alveolar edema fluid. This may be further evidence of a disturbance in the synchronizing mechanisms of the two-pump system of the heart

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1 Burch G E A primer of congestive heart failure Springfield, 1954 Charles C Thomas Publisher

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ratory related ischemia comes from the left ventricle In stress testing *both ST segment depression* and R wave amplitude are seen to fluctuate with respiration When this is observed the depth of the ST depression increases with in piration as does the amplitude of the R wave The change in R wave amplitude with in reasing stroke volume has been termed the Brody effect"[1] (Fig 1)

The above tracing is a typical example recorded on a 63-year-old man who had severe three vessel disease documented by angiography In an attempt to elucidate the mechanism left ventricular pressures at the time of severe ischemia were recorded when respiratory related ST segment depression was observed It can be seen in Fig 2 that as ST segment depression deepens it is associated with an increase in left ventricular end-diastolic pressure the most common hemodynamic correlative of myocardial ischemia It would seem obvious that when the negative pressure in the thorax produced by in piration pulls more blood into the right atrium, it must be passed on to the left ventricle This volume load then increases wall tension and produces an elevation of diastolic filling pressure when the compliance is temporarily reduced by ischemia Such a chain of events would explain the aggravation of angina reported

I would therefore disagree with the a umption made by the authors and attribute the increase in angina associated with inspiration, to be evidence of severe left ventricular ischemia and would predict that the patient not only has right coronary disease but multiple vessel involvement

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Reply

To the Editor

Dr Ellestad s observation of ST segment depression concurrent with inspiration during heart catheterization is fascinating However according to his Fig 2 the ST segment depression oc urred simultaneous with the beginning of inspiration This is the point in time that the righ t ventricle not the left would be volume loaded At least 5 and usually 7 and 8 seconds would be required for the increase in right v ntricular stroke volume to cross the lung and reach the left ventricle even in the exercising l eart Moreover during *early* inspiration, one would expect the augmented negati e intrathoracic pressure to diminish left ventricular filling by momentarily reducing pressure in the left atrium Dr Ellestad s hemodynamic and electrocardiographic observ tions do *not* fit with this expectation If the timing of inspiration in his Fig 2 is correct, then an explanation other than volume loading must be sought for ST segment depression and increase in left ventricular end-diastolic pressure during inspiration

Returning to the original communication our patient (a 4-year-ol l physician) related that his pain increased toward the end of inspiration certainly well before 7 seconds *after* right ventricular filling increases because of in piration This time sequence together with the subsequent development of inferior wall infarct is why we thought that the right ventricle might be implicated in his pain A negative stress electrocardiogram prior to his myocardial infarction and a continuing pain free clinical course even during exercise ever since his myocardial infarction makes severe multiple vessel disease unlikely

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The treadmill re examined

To the Editor

I would like to make a few comments regarding your article Now the treadmill" published in the November 1976 issue of AMERICAN HEART JOURNAL.

During the past 16 years I have had the opportunity to perform over 90 000 maximal performance treadmill stress tests This encompasses 10 years in the United States Air Force and six years of private practice in Dallas. Even though the stress tests are maximal performance there have been only five significant problems Three of these were heart attacks that occurred within 24 hours following the stress test (all survi ed without major complications) and two cases of ventricular fibrillation. In the latter cases one required electrical defibrillation and the other reverted spontaneously Both patients survived and had no further problems.

With this incidence of untoward response it does not appear that this procedure is dangerous and such stress testing should be limited to hospitals only

With the support of the Institute for Aerobics Research we are accurately quantifying and evaluating all treadmill stress testing done at the Cooper Clinic The following tables (Tables I and II) provide details on the 8 132 treadmill tests performed at the Cooper Clinic between November 1972 and December 1975 Of this total 14 per cent were abnormal with 568 (7 per cent) equivocal and 572 (7 per cent) positive Of the 7 023 with normal resting ECG s the percentage with abnormal treadmill ECG s was 10 2 per cent 5 7 per cent equivocal, and 4 4 per cent positive Since some of these were repeat tests the tables separate first from subsequent visits For the first visit population equivocal tests occurred in 260 of 5 019 cases with normal resting ECG s (5 2 per cent) and positive in 228 of 5 019 (4.5 per cent) On the first visit 9 8 per cent of males with normal resting ECG s had positive treadmill ECG s with half equivocal and half positive

In reviewing this data it is obvious that many people are totally unaware of probable heart disease since they are asymptomatic and their resting electrocardiograms are

Inspiration and angina pectoris

To the Editor

A few comments are in order concerning the article "The influence of inspiration on angina pectoris. A clue to right coronary artery disease" published in the October 1976 issue of AMERICAN HEART JOURNAL (92:537, 1976). Buda and Levene's deduction that angina aggravated by inspiration comes from the right ventricle is appealing but most likely is in error.

Repeated observations in our laboratory suggest that inspi-

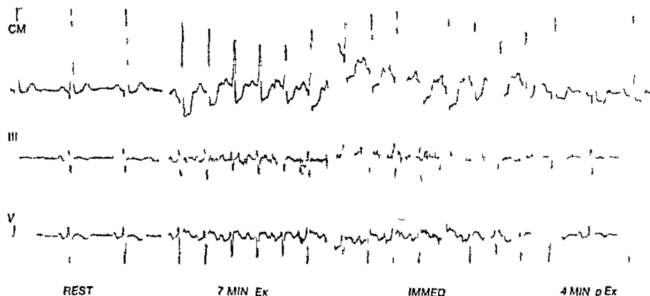


Fig. 1. Exercise tracing of a 63 year old man with severe three vessel disease. Note the increase in R wave and the associated augmentation of the S-T segment depression. The increase in R waves consistently correlated with inspiration. (From Ellestad, M. H.: Stress testing principles and practice, Philadelphia, 1975, F. A. Davis Company. Published with permission.)

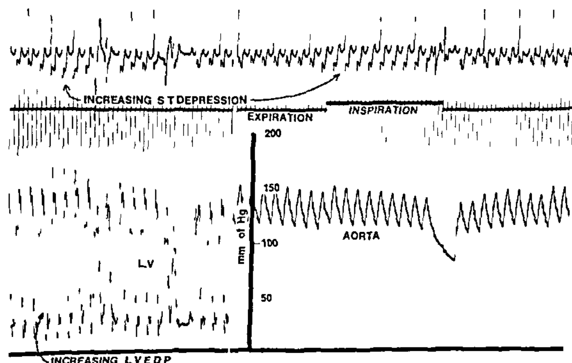


Fig. 2. Left ventricular pressure tracings in a patient with severe three vessel disease (different patient from Fig. 1) who had an increase in left ventricular end diastolic pressure with each inspiration, correlating with the increasing S-T depression on the electrocardiogram. (From Ellestad, M. H.: Stress testing principles and practice, Philadelphia, 1975, F. A. Davis Company. Published with permission.)

Anterior conduction delay

To the Editor

Anterior (left middle fascicular) delay is an important cause of prominent right precordial R waves and was properly diagnosed by Drs. Burchell and Reed (their Fig 3) in their paper on machine processed electrocardiography diagnosis

This phenomenon is often encountered in clinical electrocardiography and vectorcardiography practice and should be reported as large anterior QRS forces consistent with dorsal infarction or anterior conduction delay if right ventricular hypertrophy is clinically ruled out

The vectorcardiographic loops in such patients are indistinguishable from some cases of right ventricular hypertrophy and from most cases of true dorsal infarction When angiography and ventriculography are carried out in such patients (as in Burchell and Reed s reported case) the anterior descending artery is most commonly involved and indeed may be the only vessel involved

Of great interest in their case is the reported disappearance of the large anterior forces following bypass graft of the left anterior descending artery This certainly is consistent with a conduction delay on an ischemic basis improved after bypass

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Noise reduction in ambulatory monitoring

To the Editor

Monitoring the electrocardiogram for long periods has become a st ndard and useful diagnostic procedure Analysis by high peed scanning (Holter technique) or computer is often impeded by the presence of artifacts due to electrode movem nt Electronic filtering may improve the diagnostic yield at the price of distorting the electrocardiogram An expensi e solution is offered by computer artifact recognition programs but ever these have shortcomings

Due to the widespread use of monitoring equipment we feel that drawing attention to ar inexpensi e method of reducing artifacts at source would be of value

The origin of artifacts due to movement is complex but is mainly due to the presence of a direct potential of about 10 to 20 mV across a kin electrode electrode interface This potential is the re ultant of electrolytic effects possible leakage in the input circuitry of the amplifier and the skin potential of Tarchanoff

Movement of the electrode on the skin causes a variation in contact resistance which is reflected as a changing potential at the input terminal of the amplifier (Ohm s law) Removing the epidermis may reduce these skin potentials and resultant artifacts by a factor of 20

We clean the skin with ether to ensure adhesion A 5 mm area is marked with a colored fiber tipped pen A 6 mm diamond abrasive dental bit in a high speed (30 000 r p m.) Dremel Moto-tool (Model 258 Dremel Mfg Co Racine Wisc U.S A) is briefly touched to the marked area leaving a 2 to 3 mm spot where the coloring and therefore outer layers of epidermis have been removed Any pain experienced or blood drawn indicates that the epidermis has been penetrated and the procedure should then be repeated in an adjacent spot using less pressure on the drill

Clean silver-silver chloride cup electrodes (e g Hewlett Packard Cat No 14068) are carefully filled with electrocardiographic paste and applied to the prepared skin area with standard double sided adhesive discs The discs are then further secured with an 8 cm square self adhering foam pad (Reston brand Medical Products Division 3M Company Minnesota Mining & Manufacturing Co 3M center St Paul Minn 55 07)

The electrode wires are taped to the skin with a Reston foam pad some distance from the electrode to prevent traction being transmitted to the electrode A further precaution against displacement of the electrodes during the summer months is to harness the patient with a disposable tight fitting vest quickly and easily made from Elastomesh No 5 Smith and Nephew Ltd

Using this method we have performed over 1500 6-hour ambulant Holter tape recordings to analyze ventricular ectopic beats in postmyocardial infarction patients with less than 5 per cent of tapes showing artifacts that impede recognition of arrhythmias

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REFERENCE

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Mitral valve prolapse click syndrome in twins

To the Editor

We recently have been involved personally and professionally in the evaluation of identical twin subjects with echocardiographically documented mitral valve prolapse cli k syndrome Rarely has this problem been reported in twins and not previously with echocardiographic confirmation

Case reports

Case 1 J B G an asymptomatic currently healthy 39 year old physician without history of cardiovascular illness underwent a routine physical examination on discharge from the armed services Numerous previous phys cal examinations

Table I Treadmill ECG results, by visit, sex and resting ECG status November, 1972 to December, 1975 Percentage normal, equivocal positive and abnormal (row percentages)

	Males				*Females*				*Total group*			
	Exercise ECG				*Exercise ECG*				*Exercise ECG*			
Resting ECG	*Normal*	*Equiv*	*Pos*	*Abn*	*Normal*	*Equiv*	*Pos*	*Abn*	*Normal*	*Equiv*	*Pos*	*Abn*
First visits												
Normal	90 2	4 9	4 9	9 8	90 5	6 9	2 5	9 5	90.3	5 2	4.5	9 7
Abnormal	62 6	14 5	22 9	37 4	66 3	15 2	18 5	33 7	63 0	14 6	[illegible]	[illegible]
Total	86 8	6 1	7 1	13 2	87 9	7 8	4 3	12 1	87 0	6 3	6 7	13 0
Subsequent visits												
Normal	89 0	6 4	4 6	11 0	86 5	12 5	1 0	13 5	88 8	7 0	4 2	11 [illegible]
Abnormal	59 7	14 9	25 4	40 3	53 1	22 4	24 5	46 9	58 9	15 8	25 3	41 1
Total	84 1	7 8	8 1	15 9	80 2	14 4	5 4	19 8	83 7	8 5	7 8	16 3
All visits												
Normal	89 9	5 3	4 8	10 1	89 7	8 1	2 2	10 3	89 8	5 7	4 4	10 2
Abnormal	61 5	14 7	23 9	38 5	61 7	17 7	20 6	38 3	61 5	15 1	23 4	38 5
Total	86 0	6 6	7 4	14 0	86 1	9 4	4 5	13 9	86 0	7 0	7 0	14 0

Table II Treadmill ECG results by visit sex and resting ECG status November 1972 to December 1975 Numbers of patients in each category

	Males				*Females*				*Total group*			
	Exercise ECG				*Exercise ECG*				*Exercise ECG*			
Resting ECG	*Normal*	*Equiv*	*Pos*	*Total*	*Normal*	*Equiv*	*Pos*	*Total*	*Normal*	*Equiv*	*Pos*	*Total*
First visits												
Normal	3 852	208	209	4 269	679	52	19	750	4 531	260	278	5 019
Abnormal	379	88	139	606	61	14	17	92	440	102	156	698
Total	4 231	296	348	4 875	740	66	36	842	4 971	362	384	5 [illegible]17
Subsequent visits												
Normal	1 599	115	82	1 796	180	26	2	208	1 779	141	84	2 004
Abnormal	216	54	92	362	26	11	12	49	242	65	104	411
Total	1 815	169	174	2 158	206	37	14	257	2 021	206	188	2 415
All visits												
Normal	5 451	323	291	6 065	859	78	21	958	6 310	401	312	7 023
Abnormal	595	142	231	968	87	25	29	141	682	167	260	1 109
Total	6 046	465	522	7 033	946	103	50	1 099	6 992	568	572	8 13[illegible]

normal With this knowledge it has been possible to initiate an active intervention program changing some of their coronary risks and hopefully improving their prognosis. Regarding the latter there are several articles correlating abnormal treadmill stress tests positively with future coronary incidence

Very recently published in the proceedings of the N Y Academy of Sciences is an article entitled "The important role of fitness determination and stress testing in predicting coronary incidence [2] In this article it was quite obvious that the abnormal stress electrocardiogram was the best predictor of impending heart problems (coronary heart disease death myocardial infarction or coronary artery bypass surgery)

In summary I do feel that treadmill stress testing has great potential in diagnosing heart disease and encouraging people to become engaged in preventive or rehabilitative health care programs It is a sensitive tool that can be used accurately in epidemiological studies in predicting coronary disease There fore I was surprised to see your article and wanted you to be aware of our work

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artery disease The electrocardiogram and posteroanterior and lateral chest roentgenograms were normal. An echocardiogram showed mitral leaflet prolapse The twin s father now dead had no known evidence of cardiac click or murmur There are no other siblings.

Discussion Only two previous reports of mitral valve prolapse-click syndrome involve twins. In both sets associated congenital defects may have been present The first report concerned 17 year-old girls both with midsystolic clicks. One had a late systolic murmur and the other had aortic insufficiency Their mother also had a midsystolic click. The second twinship involved 18-year-old girls the first had a midsystolic click alone and the second had a midsystolic click and a late systolic murmur Both had high arched palates Neither parent was affected Echocardiographic data were not mentioned in either of the two accounts.

In the patients presented here the late discovery of clicks the fact that both twins had been examined previously on multiple occasions without auscultatory abnormalities and the previously normal phonocardiographic study in Patient D E G are consistent with the natural history of the disorder Uncommon and of greater note is the absence of associated skeletal abnormalities of other cardiac auscultatory or electrocardiographic findings (other than QRS amplitude in Patient D F G) and of exercise induced arrhythmias.

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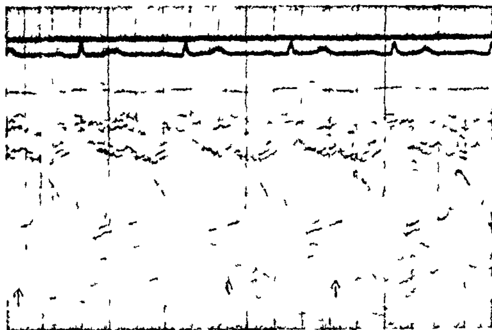


Fig 1 Echocardiogram from Case 1

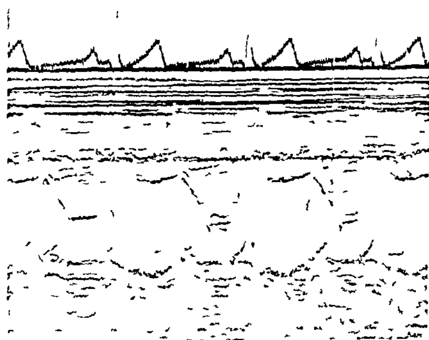


Fig 2 Echocardiogram from Case 2

in medical school had given normal findings The apical cardiac impulse was visible and palpable in the normal position There was a persistent late systolic click heard best along the left sternal border with the patient in the left lateral decubitus position No other physical abnormality was evident Posteroanterior and lateral chest roentgenograms and rest and exercise electrocardiograms yielded normal findings The echocardiogram (Fig 1) demonstrated prolapse of a mitral valve leaflet

Case 2 D E G a physician and identical twin of Patient J B G sought cardiologic evaluation because of his twin s diagnosis He also is healthy and asymptomatic Ten years earlier a phonocardiogram performed as a control part of a research project yielded normal results as did subsequent physical examinations The apical cardiac impulse was palpable in the normal position A persistent late systolic click without murmur was audible especially with the patient leaning forward Except for large QRS amplitude the resting and stress electrocardiograms showed no abnormality Posteroanterior and lateral chest roentgenograms were normal The echocardiogram (Fig 2) demonstrated mitral leaflet prolapse

Case 3 Eighteen months after identification of the twins clicks Patient M B G their healthy 74 year old mother was noted on routine examination to have a midsystolic click She had no other physical abnormality and no coronary

Books received

Fundamentals of Visceral Innervation By Budh Dev Bhagat Paul A Young and Donald E Biggerstaff Springfield Ill 19 Charles C Thomas Publisher 193 pages Price $14 75

William Harvey An Anatomical Disputation Concerning the Movement of the Heart and Blood in Living Creatures Translation and Introduction by Gweneth Whitteridge Philadelphia 1977 Blackwell Scientific Publications 147 pages Price $14 00

Low Density Lipoproteins Edited by Charles E Day and Robert S Levy New York 1977 Plenum Publishing Corporation 433 pages Price $39 50

Beta adrenergic Blockers and Hypertension Edited by D Ganten R Dietz B Luth and F Gross Stuttgart Germany 1976 Georg Thieme Verlag 201 pages

ABC de Soins Intensifs Cardiologiques By R Rullière and D Safran Paris 1977 Editions Masson 128 pages Price 34 Francs

The Broken Heart The Medical Consequences of Loneliness By James J Lynch New York 1977 Basic Books Inc., 238 pages Price $10 9

The Patient s Guide to Surgery By Lawrence Galton New York 1977 Avon Books 445 pages Price $2 50

Current Concepts in Radiology vol three Edited by E James Potchen MD St Louis 1977 The C V Mosby Company 477 pages Price $39 50

The Biochemistry of Smooth Muscles Edited by Newman L Stephens MD Baltimore 1977 University Park Press 718 pages Price $34 50

Book reviews

Coronary Artery Disease—Major Problems in Internal Medicine volume XI By Richard Gorlin M D Philadelphia 1976 W B *Saunders Company* 317 *pages* Price $16 50

This is the eleventh volume on *Major Problems in Internal Medicine* This subject is an extremely important one The approach to the subject of coronary artery disease is the one in general use today in which coronary angiography and ventric ulography are emphasized For example the author begins the book with a discussion of these two technics rather than with the history and physical examination of the patient Such is the direction of modern cardiology The author states in the *first sentence of the Preface that The time has come for an* aggressive approach to coronary heart disease and that aggressive technologic approach is reflected throughout the book The average family physician will find this book difficult to follow whereas the young trainee and technologist will find the book summarizes very well the modern and aggressive approach to the management of coronary heart disease

Gorlin describes coronary angiography ventriculography pain syndromes pathogenesis of atherosclerosis coronary anatomy pharmacotherapy revascularization therapy etc very well from his own experiences and from the experiences of those who employ the aggressive approach The principles for the selection of surgical therapy are supported to a great *extent from published data from the Cleveland Clinic (Figs* 15 2 15 3 15 4) which do not reflect the results of the USA at large Regardless this is a concise presentation of the present day aggressive approach to the *management of coronary* artery disease which presents these practices and principles very well

Microcirculation Transport Mechanisms—Disease States Edited by John Grayson and Walter Zingg New York 1976 Plenum Press 361 pages Price $32 00

This book consists of the papers presented at the First World Congress for the Microcirculation held in Toronto during June 1975 The book is divided into ten parts with several papers each Among the parts are presentations on capillary transport and exchange molecular and oxygen transport effect of shock on capillary transport shock and the microcirculation *ischemic and graft rejection trauma and* inflammation and others Each paper is short and succinct and clearly presented This book should interest all cardiolo *gists physiologists and cardiac surgeons* since the small coronary vessel are similar in many respects to the microcir culation elsewhere This is a valuable publication

Echocardiography A Teaching Atlas By Joel M Felner M D and Robert C Schlant M D New York 1976 Grune & Stratton Inc 562 pages Price $38 50

Echocardiography (ECHO) is a rapidly growing diagnostic procedure in cardiology This book is another fine publication on the subject The book really adds nothing especially new to the medical literature but it does present another approach to the presentation of echocardiography for tho e who are already responsible for the procedure in hospitals and clinics

The tables and references of the appendix are important and contain values of measurement generally used in he field But as is evident the accuracy of measurements obtained by ECHO is debatable For example Table 12 on page 5?1 lists the thicknesses of the IV septum and the posterior wall of the heart However no data are reported in the book to support the accuracy of these measurements This is not a critici m of the book but a statement of fact for the entire field of ECHO

The illustrations are clear and the legends informative This teaching atlas is a good publication and a fine source for the study and learning of ECHO It is recommended to all physicians who interpret the ECHO

Non Invasive Diagnostic Techniques in Cardiology By Alberto Benchimol M D Baltimore 1977 The Williams & Wilkins Company 444 pages Price $29 50

This is another book on non invasive diagnostic techniques in cardiology This one summarizes Benchimols 14 years experience with these techniques including a study of 2 000 *echocardiograms recorded during the* past two years The book of about 450 pages includes 13 chapters concerned with auscultation and phonocardiography ultrasound pul e waves disease of the valves prosthetic valves and the common diseases of the heart The book as would be expected adds nothing especially new to the medical literature except the author s experience The recordings illustrated are of high quality and the di cussions *lucid but not critical Readers* without clinical experience probably will develop the opinion that good clinical cardiology cannot be performed without the fairly routine use of these non invasive and relatively expen sive methods It is unfortunate that these techniques receive such emphasis and are employed so extensively in clinical cardiology Nevertheless readers will find this book a reliable source of information about the non invasive recording methods used rather extensively in cardiology There are specific details of the book which need modification when a second edition is published *Because of the emphasis on the* e many technics in cardiology those in training will find this to be a good source of information related especially to interpre tation of recordings

Pericardial Diseases Edited by David H Spodick Philadel phia 1976 F A Davis Company 308 pages Price $30 00

This issue on pericardial disease of the series of *Cardiovas cular Clinics* is another very good one Spodick is the guest editor with many *outstanding contributors writing* interesting and practical clinical papers on various aspects of pericarditis The book should have included a discussion of the surgically produced pericarditi of coronary bypass operations Thi type of pericarditis is being produced by the thousands each year in the USA alone This needs serious consideration Neverthe less this is an excellent clinical review of pericarditis and the book is worth owning by all internists *cardiologists* and cardiac surgeons Physicians will profit from a study of this publication

Books received

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Selected topics in cardiology

The University of Texas Health Science Center at Houston, Division of Continuing Education will present a three-day seminar on selected topics in cardiology in Houston, Texas, on December [illegible] through [illegible] 1977. The 23rd annual James J and [illegible] Truitt Lecturer for 1977 is Dr Leonard Dreifus, Chief, Division of Cardiology, Lankenau Hospital, Philadelphia. Dr Dreifus will lecture on various aspects of cardiac arrhythmias including interpretation and treatment of arrhythmias, junctional arrhythmias and ventricular arrhythmias. The W P W syndrome, pacemaking problems and drug management of various cardiac arrhythmias will also be discussed.

For further information on this seminar, please contact Office of the Director, The University of Texas Health S[illegible] Center at Houston, Division of Continuing Education, Box 20[illegible], Houston, Texas [illegible]

Cardiovascular System Dynamics conferen[illegible]

The third International Conference on Cardiov[illegible] System Dynamics will be held in Leiden, The Netherla[illegible] August 2[illegible] through 31, 197[illegible]. Major theme of the conf[illegible] will be Basic and Clinical Aspects of Cardiac Dynami[illegible] further information regarding the conference please c[illegible] Dr A C Arntzenius or Dr J Baan, Department of Ca[illegible]ogy, University of Leiden, Leiden, The Netherlands.

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Announcements

Selected topics in cardiology

The University of Texas Health Science Center at Houston Division of Continuing Education will present a three day *seminar on selected topics in cardiology in Houston Texas* on December 6 through 8 1977 The 23rd annual James J and Una Truitt Lecturer for 1977 is Dr Leonard Dreifus Chief Division of Cardiology Lankenau Hospital Philadelphia Dr Dreifus will lecture on various aspects of cardiac arrhythmias including interpretation and treatment of arrhythmias junctional arrhythmias and ventricular arrhythmias The WPW syndrome pacemaking problems and drug management of various cardiac arrhythmias will also be discussed

For further information on this seminar please contact Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education PO Box 20367 Houston Texas 77025

Cardiovascular System Dynamics conference

The third International Conference on Cardiovascular System Dynamics will be held in Leiden The Netherlands on August 27 through 31 1978 Major theme of the conference will be Basic and Clinical Aspects of Cardiac Dynamics For further information regarding the conference please contact Dr A C Arntzenius or Dr J Baan Department of Cardiology University of Leiden Leiden The Netherlands

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